PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 24 JAN 2006
WIPO PCT

Applicant's or agent's file reference 50375C:MOB	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/AU2004/001368	International filing date *(day/month/year)* 7 October 2004	Priority date *(day/month/year)* 7 October 2003

International Patent Classification (IPC) or national classification and IPC

Int. Cl. ***C07D 207/34*** (2006.01) (continued in supplemental box)

Applicant

UNIVERSITY OF WESTERN SYDNEY et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of **32** sheets, as follows:
      - [X] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

Date of submission of the demand 21 March 2005	Date of completion of this report 10 January 200610 January 200610 January 200611 January 2006
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer O.L. CHAI Telephone No. (02) 6283 2482

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/001368

Box No. I Basis of the report

With regard to the language, this report is based on:

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

- [ ] international search (under Rules 12.3(a) and 23.1 (b))
- [ ] publication of the international application (under Rule 12.4(a))
- [ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[ ] the international application as originally filed/furnished

[X] the description:

pages **1-61** as originally filed/furnished
pages* **62-65** received by this Authority on **20 July 2005** with the letter of **19 July 2005**
pages* received by this Authority on with the letter of

[X] the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* **66, 67, 69, 70, 72** received by this Authority on **20 July 2005** with the letter of **20 July 2005**
pages* **68, 71, 73, 74** received by this Authority on **23 December 2005** with the letter of **23 December 2005**

[X] the drawings:

pages as originally filed/furnished
pages **1/19-19/19** received by this Authority on **14 December 2004** with the letter of **14 December 2004**
pages* received by this Authority on with the letter of

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

- [ ] the description, pages
- [ ] the claims, Nos.
- [ ] the drawings, sheets/figs
- [ ] the sequence listing *(specify)*:
- [ ] any table(s) related to the sequence listing *(specify)*:

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- [ ] the description, pages
- [ ] the claims, Nos.
- [ ] the drawings, sheets/figs
- [ ] the sequence listing *(specify)*:
- [ ] any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-19	YES
	Claims		NO
Inventive step (IS)	Claims	1-19	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-19	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1 WO 1998/049142
D2 WO 2003/041128
D3 US 4942227
D4 WO 1999/062551
D5 WO 2003/020877
D6 Arzneimittel-Forschung (2003), 53(2), 107-113
D7 Bioorganic & Medicinal Chemistry (2002), 10(10), 3313-3318
D8 Nucleic Acids Research (2000), 28(24), 4856-4864
D9 European Journal of Biochemistry (1999), 266(2), 392-402
D10 Journal of the American Chemical Society (1999), 121(6), 1113-1120
D11 Medicinal Chemistry Research (1996), 6(6), 365-371
D12 Tetrahedron (1994), 50(42), 12065-84
D13 Bioorganic & Medicinal Chemistry Letters (1993), 3(8), 1751-6
D14 Journal of the American Chemical Society (1987), 109(24), 7564-6

As a result of the amendments, none of the cited documents discloses or fairly suggests the invention as claimed. Therefore, claims 1-19 are considered to meet the requirements of Article 33(2)-(3) PCT with regard to novelty and inventive step.

Claims 1-19 are considered to meet the requirements of Article 33(4) of the PCT with regards to industrial applicability.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Claims 1-12 and 16-19 are not fully supported by the description. The scope as defined by the said claims extends far beyond what has been disclosed in the description. From a fair reading of the specification, there is only substantial support for a small number of compounds – there are only 4 examples of the compounds claimed. The claims should be drafted to clearly reflect what has been disclosed.

2. Claims 1 and 9 are not clear in scope.
   (i) The variables M^1, M^2 and M^3 are merely defined by results, it is not clear what metal coordination complex can be included.
   (ii) The variables T^1, T^2 and T^3 have not been defined clearly except that it is a linker group. It is not clear what can be included.
   (iii) The term "sequence selective" does not seem to have a clear definition and it is not clear what pyrrole imidazole polyamides fall within the scope and what are excluded.

3. Claim 7 is not fully supported by the description. The definition of the linker groups includes many linkers that the specification does not have any support for.

4. Claim 17 is not clear. It is not clear what can be included in the terms "therapeutic agent", 'reporter group" and "a sequence". These imprecise terms render the scope unclear.

5. Claim 19 is not clear. It does not define clearly what the method of diagnosis actually diagnoses.

upplemental Box

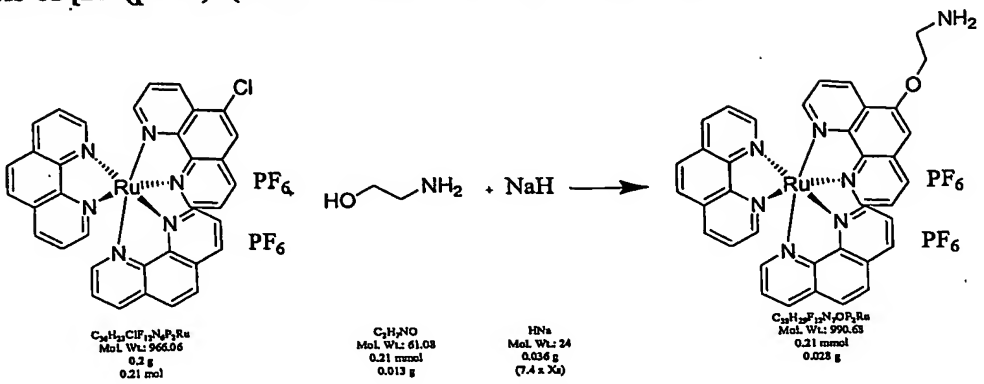
ı case the space in any of the preceding boxes is not sufficient.

ontinuation of: IPC Classification

ıt. Cl.

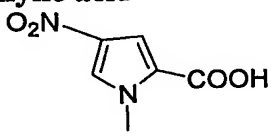
|61K 31/4164 (2006.01)
|61K 31/40 (2006.01)
|61P 31/12 (2006.01)
A61P 31/18 (2006.01)
A61P 35/00 (2006.01)
C07D 209/56 (2006.01)
C07D 233/90 (2006.01)

Synthesis of $[Ru(phen)2(Phen\text{-}4\text{-}NH_2\text{-}CH_2CH_2\text{-}NH_2)](PF_6)_2$



The ruthenium complex, $[Ru(phen)_24\text{-}Cl\text{-}Phen](PF_6)_2$ (0.2 g, 0.21 mmol) was also suspended in deaerated DMF (5 mL) while separately NaH (0.036 g, 1.5 mmol) was also suspended in a stirring solution of dry, deaerated DMF (5 mL). Ethanolamine (12.8 µL, 0.21 mmol) was added to the solution of NaH. The two solutions were mixed via cannula and the resulting black solution heated at 40 °C for 2 hr. The solution was evaporated to dryness under reduced pressure leaving a red black residue which was purified by flash chromatography on silica gel, eluting with acetonitrile (5% saturated KNO_3 solution and 10 % water). Fractions containing unreacted starting complex and product were isolated by TLC (SiO_2, ACN/5% saturated KNO_3/10% H_2O). These fractions were combined, reduced to dryness then extracted into dichloromethane (4 x 100 mL) from H_2O (100 mL). The extracts were reduced to dryness and subsequently purified on a column of TLC grade silica gel (ACN/1% saturated KNO_3/10% H_2O). This purification achieved a separation of bands containing unreacted starting complex and product. The product (band 2) was collected, reduced to dryness then extracted into dichloromethane (4 x 100 mL) from H_2O (100 mL). Evaporation of the solution to dryness under reduced pressure gave the product as a deep red solid. ^1H NMR (CD_3CN): 8.54 (d, 4H), 8.44 (dd, 2H), 8.28 (d, 1H), 8.23 (s, 4H), 8.18 (d, 1H), 8.08 (d, 1H), 8.00 (d, 1H), 7.83 (d, 1H), 7.76 (d, 1H), 7.65 (bm, 4H), 7.40 (dd, 1H), 6.70 (d, 1H), 6.38 (d, 1H), 1.30 (bs, 4H).

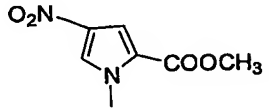
1-Methyl-4-nitropyrrole-2-carboxylic acid



Acetic anhydride (20 mL) was treated with nitric acid (4.0 mL, 70%) and the mixture heated to 50 °C for 15 min then cooled to room temperature, and slowly added to a suspension of of 1-methyl-2-pyrrolecarboxylic acid (4 g , 15.98 mmol) in of Ac_2O (12 mL) cooled to -25 °C. The mixture was stirred at -15 °C for 0.5 hr, then the temperature

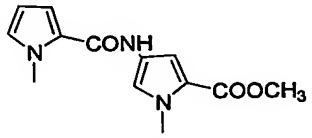
was allowed to rise to ambient, and stirring was continued for 20 min. The mixture was again cooled to -25 °C and the precipitate collected in a funnel cooled with dry ice, the solid was washed with a small quantity of cold Ac_2O (-25 °C). The crystalline solid was taken up in water containing NaOH (1 g). Acidification with the HCl precipitated the pure compound. NMR as previously reported.

Methyl 1-methyl-4nitropyrrole-2-carboxylate



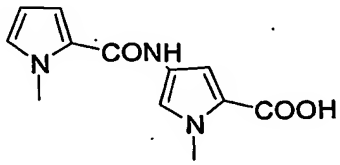
A cold solution of H_2SO_4 (2.9 mL) in MeOH (28.96 mL) was added to 1-methyl-4-nitropyrrole-2-carboxylic acid (2.897 g, 2.35 mmol). The mixture was refluxed for 24 hr. Water was added and the mixture extracted $CHCl_3$. The organic layer was dried ($MgSO_4$), and the solvent evaporated under vacuum to afford the creamy white product. NMR as previously reported.

Py/Py-COOCH$_3$



Methyl *N*-methyl-4-nitro pyrrole-2-carboxylate (0.5 g, 27.17 mmol) in MeOH (64 mL) and Pd/C (10%, 6 mg) was stirred under H_2 (1 atm) until the TLC showed no starting material (1 hr). The mixture was filtered through celite to remove the catalyst and DMF was added (3 mL). MeOH was removed under vacuum. N-methyl pyrrole-2-carboxylic acid (1.3 mol equiv) was added followed by HOBT (88 mg, 1.5 mol equiv), TBTU (209 mg, 1.5 equiv) and Et_3N (220 mg, 5 equiv). The solution was stirred for 1 hr at room temperature and the solvent removed under vacuum. The residue was purified by flash chromatography (100% DCM).

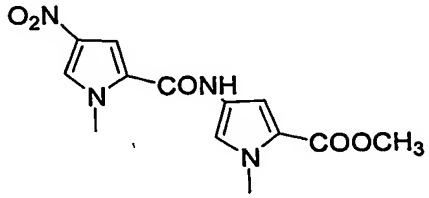
Py/Py-COOH



Py/Py-COOCH$_3$ (360 mg, 1.38 mmol) in THF/MeOH (1.1 / 7.5 mL) was added LiOH (1 M, 5.5 mL) and the solution stirred at 60 °C (oil bath) for 1.5 hr and monitored by TLC (10%, MeOH/CH_2Cl). The organics were evaporated under vacuum, the solution

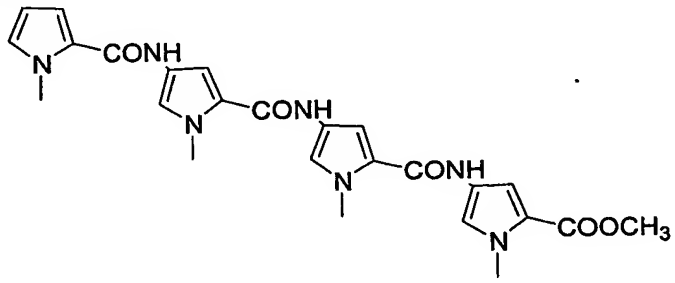
cooled and acidified with HCl (1 M 5mL). The solid was collected and air dried and left in a desiccator under vacuum overnight. NMR as previously reported.

NO_2-Py/Py-$COOCH_3$



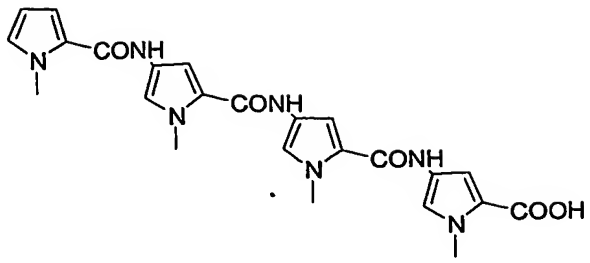
NO_2-Py-$COOCH_3$ (1.45 g, 7.83 mmol) in MeOH (150 mL) and Pd/C (174 mg) was stirred under H_2 (1 atm) for 1 hr. The mixture was the filtered through celite and DMF (3 mL) added. MeOH was removed under vacuum. NO_2-Py-COOH (1.8 g,) was added followed by HOBT (255.2 mg, 1.89 mmol) and TBTU (606 mg, 1.89 mmol) and Et_3N (638 mg, 6.32 mmol). The solution was stirred for 1 hr at room temp and the solvent (DMF) removed under vacuum until a small quantity remained. The pure compound was precipitated by addition of MeOH. %). ^1H NMR (d-DMSO): 10.21 (s, 1H), 8.15 (d, 1H), 7.53 (d, 1H), 7.43 (d, 1H), 6.88 (d, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 3.73 (s, 3H).

Py/Py/Py/Py-$COOCH_3$



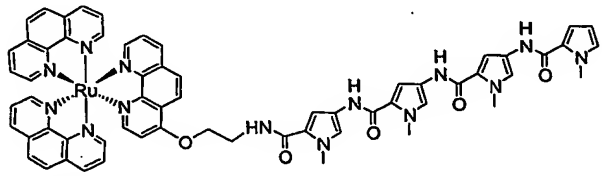
NO_2-Py/Py-$COOCH_3$ (213 mg, 0.69 mmol) was dissolved in DMF (25 mL) and added Pd/C catalyst (15 mg) and stirred under H_2 until the amine was formed. The mixture was filtered through celite and Py/Py-COOH (166 mg, 0.66 mmol) added to the solution followed by HOBT (22 mg, 0.16 mmol), TBTU (51 mg, 0.16 mmol) and Et_3N (53 mg, 0.52 mmol). The reaction was then left to couple for 1.5 hr. The DMF was removed under reduced pressure to yield the compound.

Py/Py/Py/Py-COOH



$Py/Py/Py/Py\text{-}COOCH_3$ (100 mg, 0.20 mmol) in DMF (10 mL) was added NaOH (0.75 mL) and the solution stirred at 60 °C for 1 hr. The organics were evaporated until approx. 3 mL remained and acidified with HCl (1 M, 5 mL) to yield the product.

$[Ru(phen)_2(phen\text{-}4\text{-}O\text{-}CH_2CH_2NHCO\text{-}Py/Py/Py/Py](PF_6)_2$



$[Ru(phen)_2(phen\text{-}4\text{-}O\text{-}CH_2CH_2NH_2](PF_6)_2$ (28 mg, 0.03 mmol)dissolved in DMF (25 mL) and added Pd/C catalyst (15 mg) and stirred under H_2 until the amine was formed. The mixture was filtered through celite) and Py/Py/Py/Py-COOH (75 mg, 0.15 mmol) added to the solution followed by HOBT (22 mg, 0.16 mmol), TBTU (51 mg, 0.16 mmol) and Et_3N (53 mg, 0.52 mmol). The reaction was then left to couple for 2 hr. The DMF was removed under reduced pressure to yield the compound.

The claims defining the invention are as follows:

1. A compound of formula (1)

$$[M^1\text{-}T^1]_a\text{-}[P^1\text{-}T^2\text{-}M^2]_b\text{-}[T^3\text{-}P^2]_c \qquad (1)$$

or a salt thereof,

wherein

M^1 and M^2 are the same or different and are each a metal coordination complex, wherein at least one of M^1 and M^2 is capable of interacting with a major groove or minor groove of a polynucleotide;

P^1 and P^2 are the same or different and are each a sequence selective pyrrole-imidazole polyamide;

T^1, T^2 and T^3 are the same or different and are each a linker group;

a is 0, or 1;

b is an integer selected from 1, 2, 3, 4 and 5;

wherein when b is an integer greater than 1, each P^1, each T^2 and each M^2 may be the same or different; and

c is 0, 1 or 2; wherein when c is 2, each P^2 may be the same or different and each T^3 may be the same or different.

2. A compound according to claim 1, a = 0, b = 1, and c = 0.

3. A compound according to claim 1, wherein M^1 and M^2 are the same or different and are individually selected from a platinum complex, a palladium complex, a ruthenium complex, and a rhodium complex.

4. A compound according to claim 1, wherein M^1 and M^2 are independently selected from cis -$Pt(NH_3)_2Cl$ and trans -$Pt(NH_3)_2Cl$.

5. A compound according to claim 1, wherein each pyrrole-imidazole polyamides (P^1, P^2) independently comprises a plurality of heterocyclic rings selected from the group consisting of optionally substituted N-methylimidazole (Im), optionally substituted N-methylpyrrole (Py) and optionally substituted 3-hydroxy N-methylpyrrole (Hp).

6. A compound according to claim 5, wherein each pyrrole-imidazole polyamide independently comprises 3 heterocyclic rings or 4 heterocyclic rings.

7. A compound according to claim 1, wherein the linker groups (T^1, T^2, T^3) are the same or different and each has the formula (2):

$$-Y^1\text{-}(A)_n\text{-}Y^2\text{-} \qquad (2)$$

wherein

Y^1 and Y^2 may be the same or different and are independently selected from NH, $-NH_2$, C=O, C=S, C=NH, O, OH, S, SH, S(O), $S(O)_2$, NR^3, NHR^3, $N(R^3)_2$, an optionally substituted cycloalkylamine, an optionally substituted cycloalkyldiamine, and an optionally substituted heteroaryl group (e.g., an optionally substituted N-heteroaryl group such as pyridyl, phenanthrolinyl, 2,2'-bipyridyl); where each R^3 is independently selected from alkyl, cycloalkyl, aryl or heteroaryl;

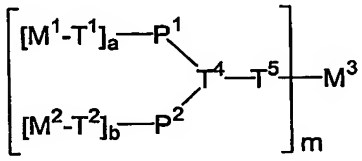
A is selected from an optionally substituted C_{1-10} alkylene, an optionally substituted C_{2-10} alkenylene, an optionally substituted C_{2-10} alkynylene, an optionally substituted C_{3-6} cycloalkylene, an optionally substituted C_{6-10} aryl, C=O, C=S, and C=NH, NH, O, S, NH_2, OH, SH, S(O), $S(O)_2$, amino acids, and spermidine; and

n is an integer selected from 1 to 20,

wherein when n is an integer greater than 1, each (A) group may be the same or different.

8. A compound according to claim 7, wherein each linker group independently comprises a group selected from $-NH-(CH_2)_n-NH_2-$, $-NH-CH_2CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2-O-CH_2CH_2CH_2-NH_2$, $-NH-C(O)-CH_2CH_2-NH-C(O)-CH_2CH_2CH_2NH_2-$, $-S-(CH_2)_n-O-(CH_2)_n-S-$, or $-NH-(CH_2)_n-O-$, and $-C(O)-NH-CH_2-C(O)-NH-CH(CH_2SH)-C(O)-NH-$, where n is an integer from 1 to 20.

9. A compound of formula (3):



(3)

where

M^1, M^2, M^3 are the same or different and are each a metal coordination complex as defined for M^1 and M^2 of formula (1) in claim 1, wherein at least one of M^1, M^2 and M^3 is capable of interacting with a major groove or minor groove of a polynucleotide;

P^1 and P^2 are the same or different and are each a sequence selective pyrrole-imidazole polyamide as defined for formula (1) in claim 1;

T^1 and T^2 are the same or different and are each a linker group of formula (2) as defined for formula (1) in claim 1;

T^5 is a linker group of formula (2) as defined for T^1 and T^2 of formula (1) in claim 1, wherein one of Y^1 and Y^2 is bound to a metallocomplex M^3 and the other of Y^1 and Y^2 is covalently bound to T^4;

T^4 is a linker group of formula (2) as defined for T^1 and T^2 of formula (1) in claim 1, wherein Y^1 is covalently bound to a pyrrole-imidazole polyamide, Y^2 is covalently bound to a pyrrole-imidazole polyamide, and wherein one Y^1, Y^2 and A is covalently bound to T^5;

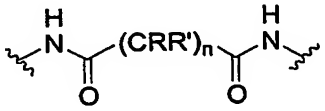
a and b are independently selected from 0 and 1; and

m is 1, 2, 3 or 4.

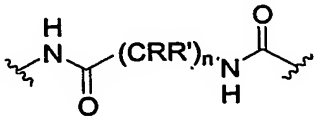
10. A compound according to claim 9, wherein m is 1 or 2.

11. A compound according to claim 9, wherein a = 0, b = 1, and m = 1.

12. A compound according to claim 9, wherein T^4 comprises



or

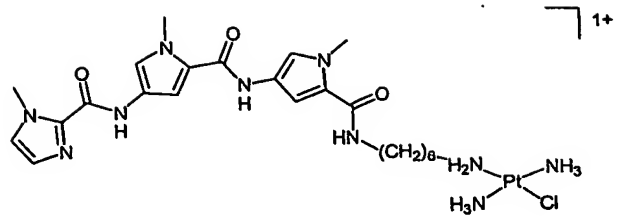


wherein n is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10,

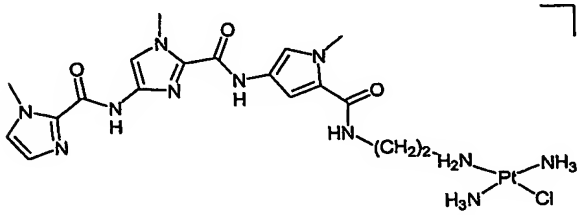
each (CRR') is independently an optionally substituted alkylene; and

wherein in one (CRR'), R' is absent and CR is covalently bound to T^5.

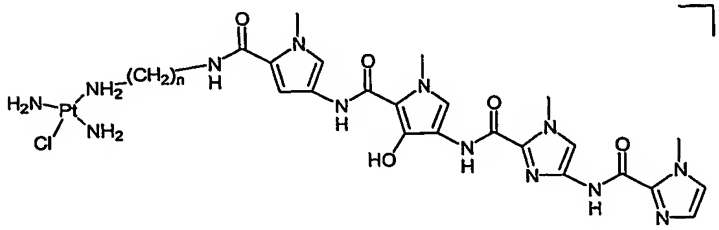
13. A compound according to claim 1, wherein said compound is selected from



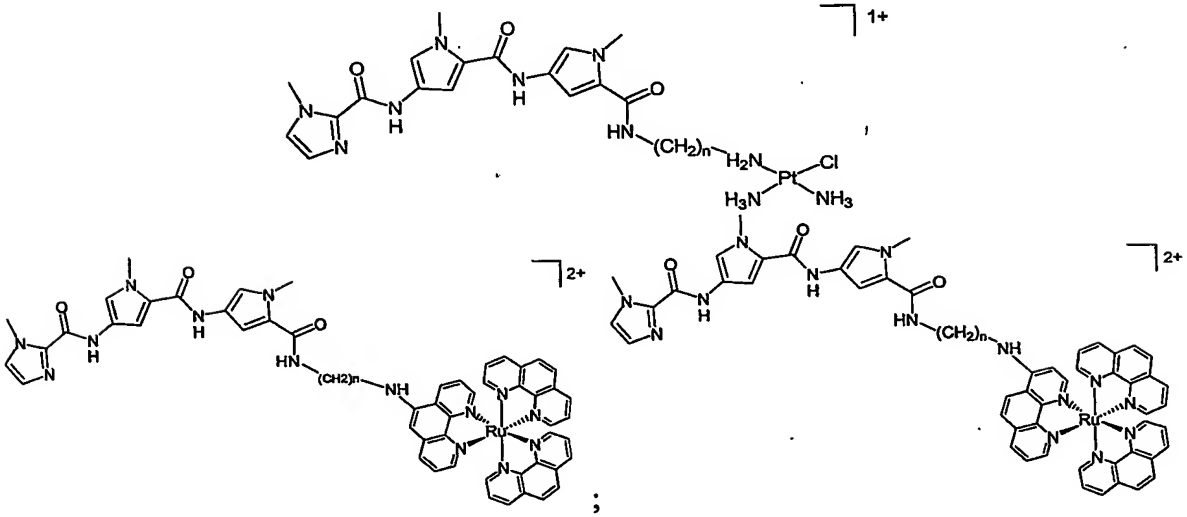
"trans-Im/Py/Py-[CONH$(CH_2)_6$-NH_2)Pt$(NH_3)_2$Cl";



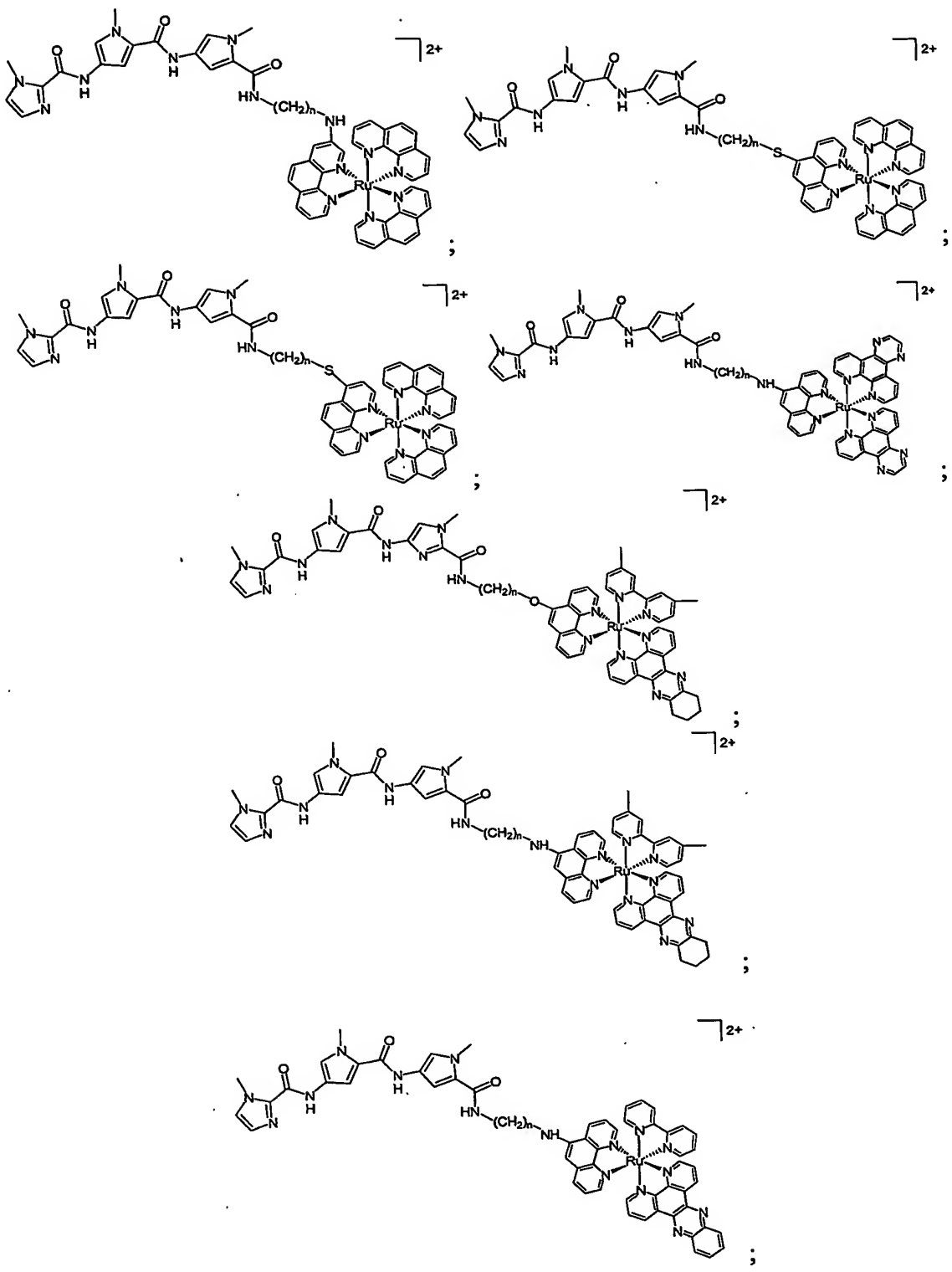
"trans-Im/Py/Py-[CONH$(CH_2)_2$-NH_2)Pt$(NH_3)_2$Cl";

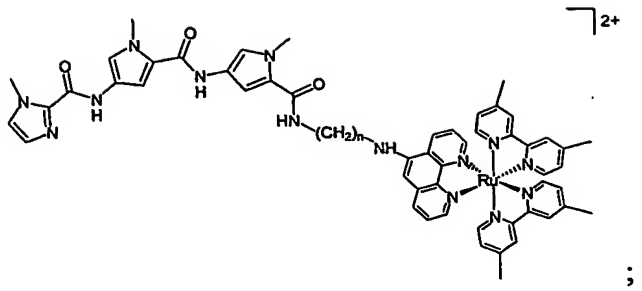


;

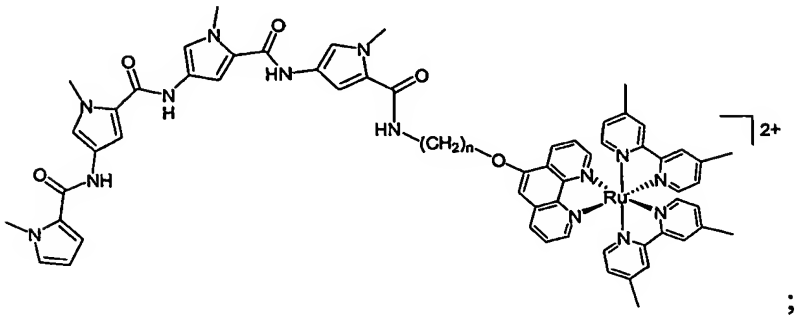


;



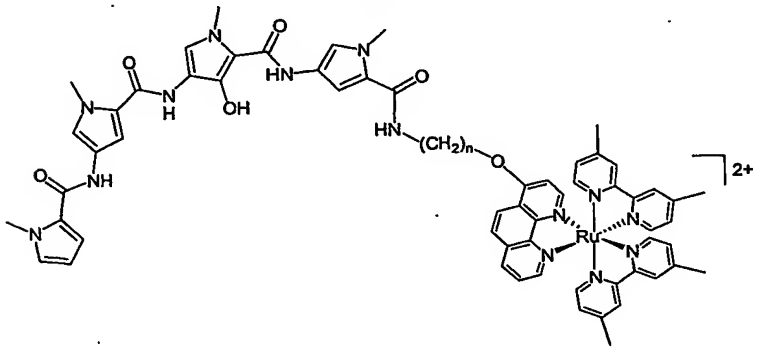


;



;

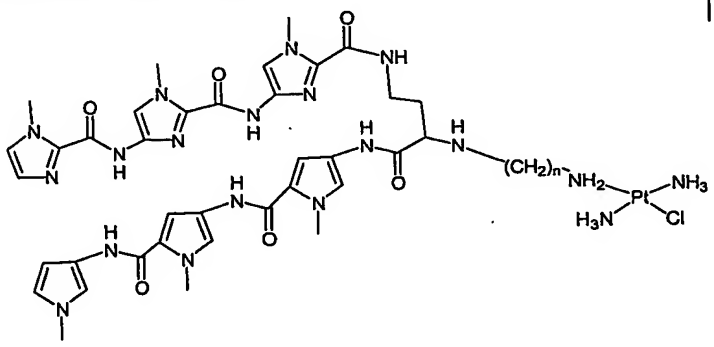
and

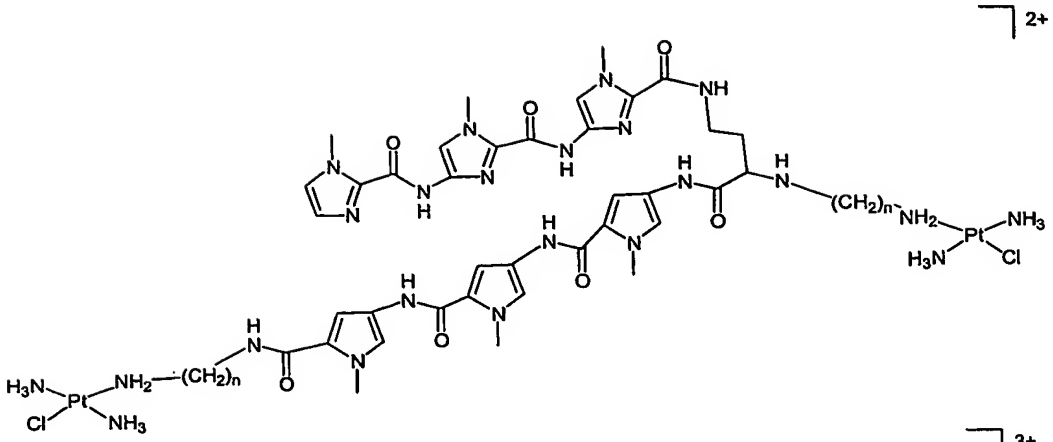


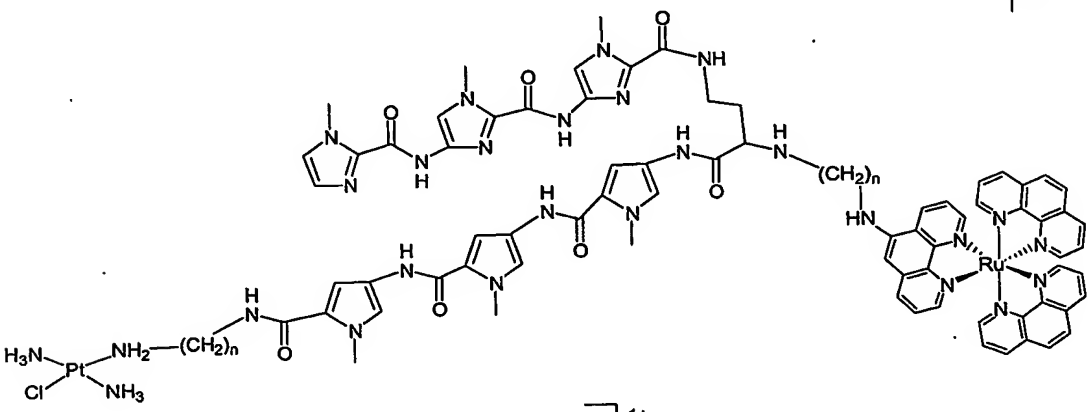
;

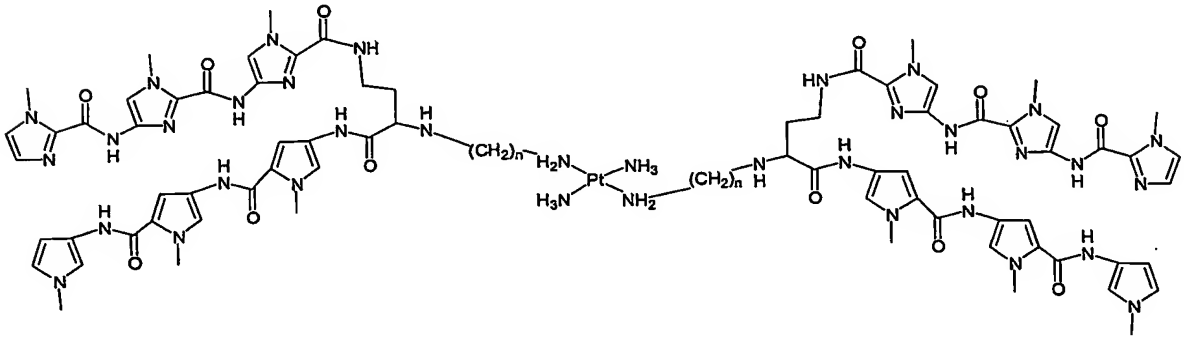
where n is an integer selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, or a salt thereof.

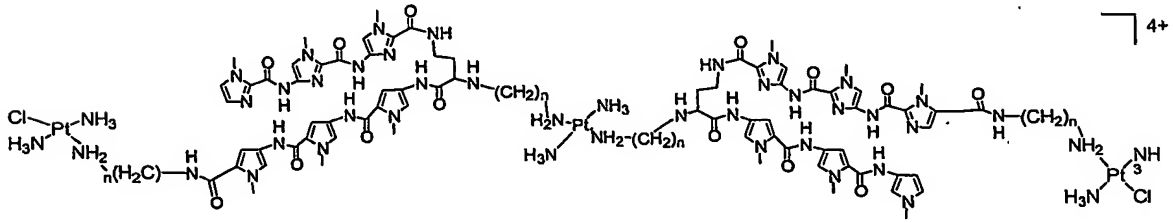
14. A compound according to claim 9, wherein said compound is selected from



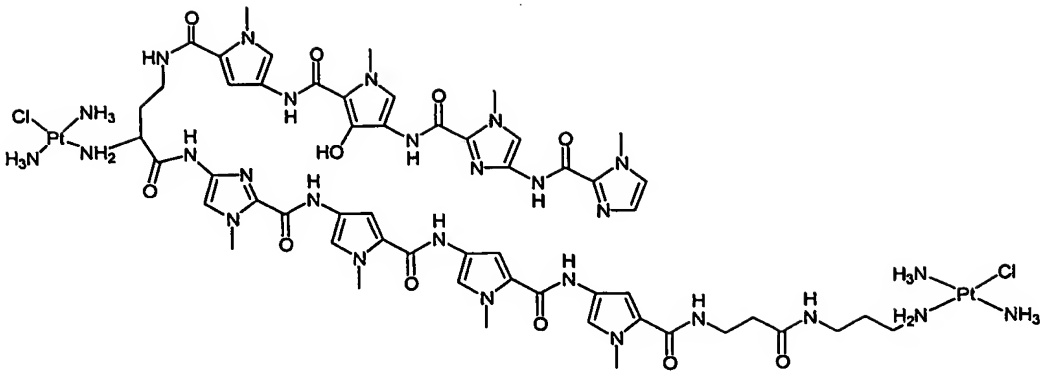






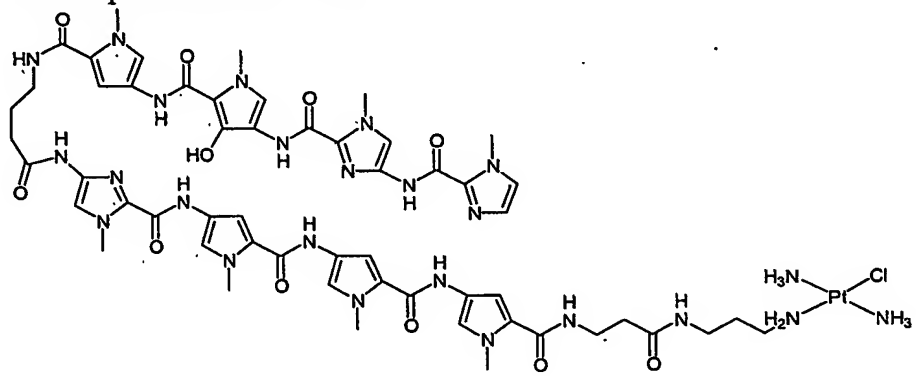


and

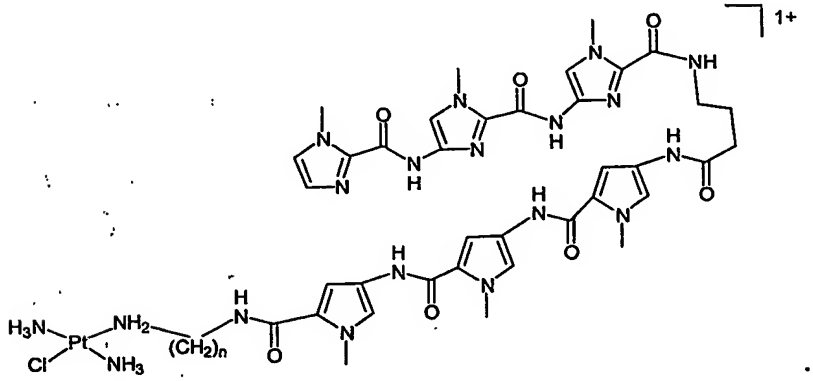


where each n is an integer independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, or a salt thereof.

15. A compound selected from



and



where each n is an integer independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, or a salt thereof.

16. A pharmaceutical composition comprising at least one compound selected from a compound of formula (1) according claim 1, a compound of formula (3) according to claim 9, and a compound according to claim 15, together with a pharmaceutically acceptable diluent, adjuvant or carrier.

17. A method of targeting a therapeutic agent(s) and/or a reporter group(s) to a sequence in a polynucleotide comprising contacting biological material suspected of containing said sequence with a compound of formula (1), formula (3) or claim 15.

18. A method of treating a disease selected from cancer, HIV and Hepatitis C, said method comprising administering to a mammal in need of such treatment a therapeutically effective amount of at least one compound according to claim 1, claim 9 or claim 15, or a pharmaceutical composition according to claim 16.

19. A method of diagnosis comprising contacting a biological sample with a diagnostically effective amount of at least one compound according to claim 1, claim 9 or claim 15, or a pharmaceutical composition according to claim 16.

Dated 22 December, 2005
University of Western Sydney

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

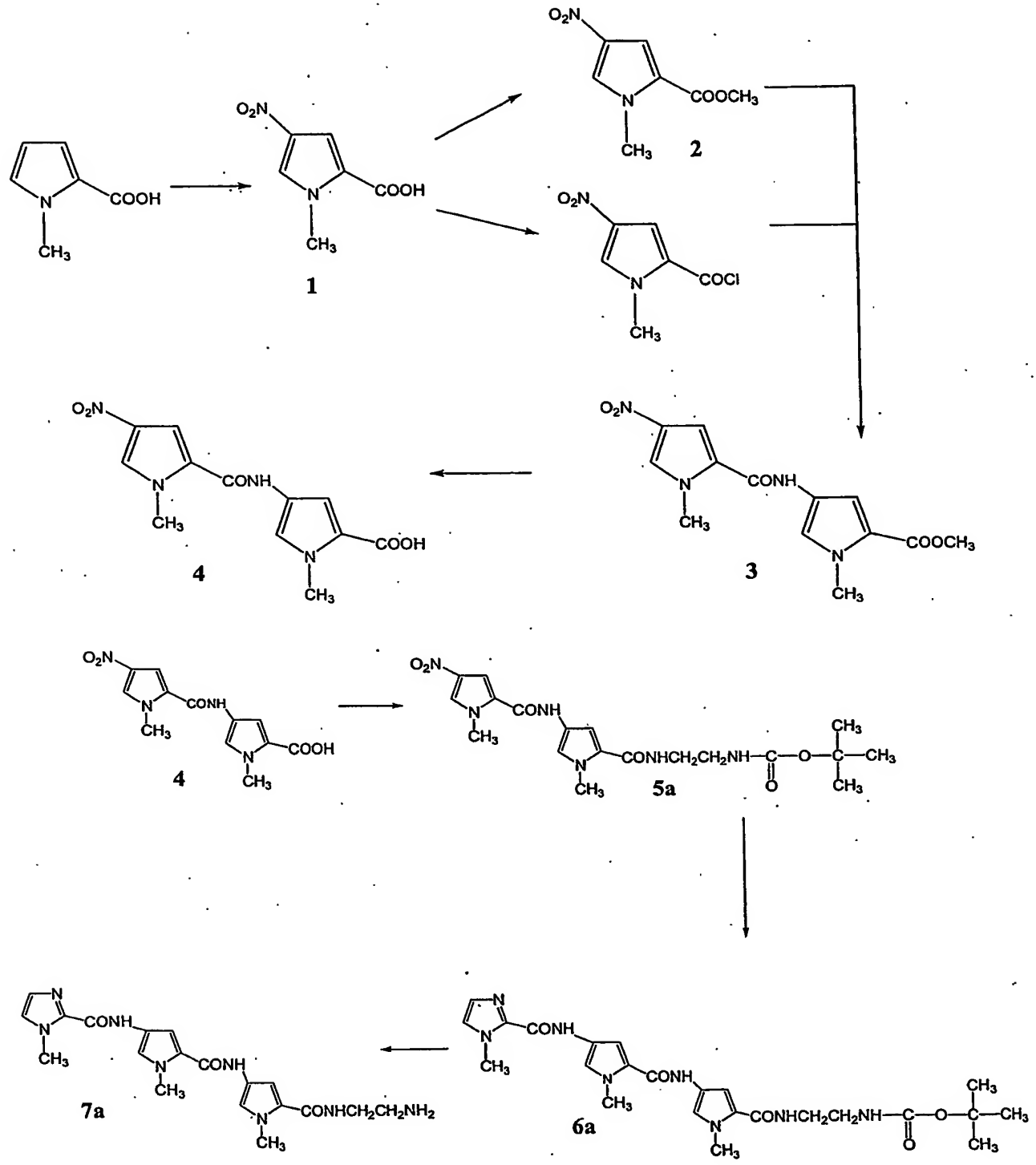
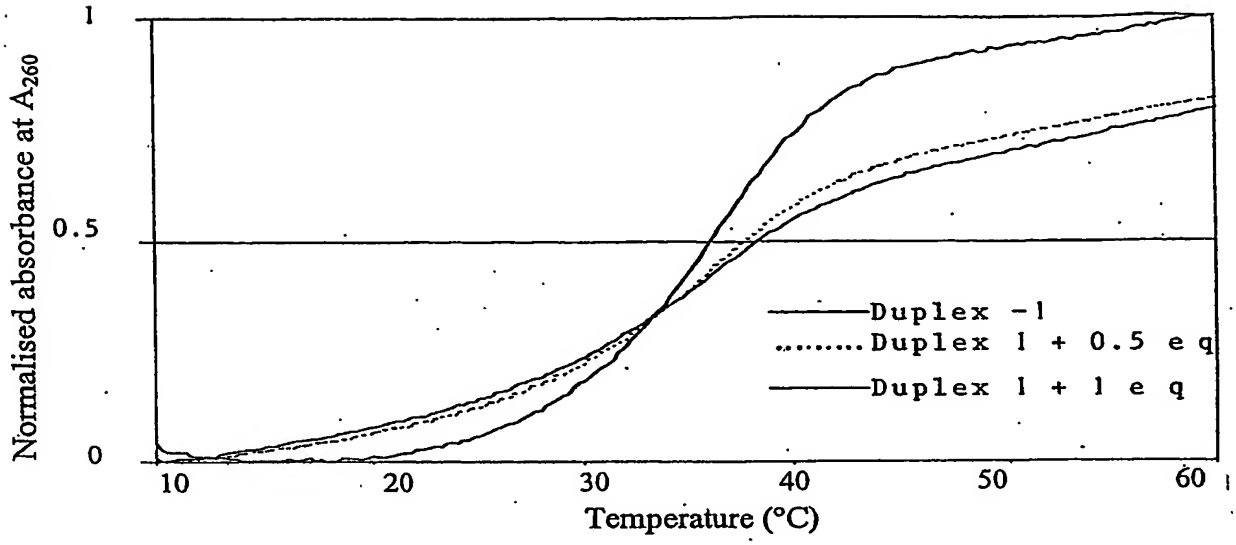
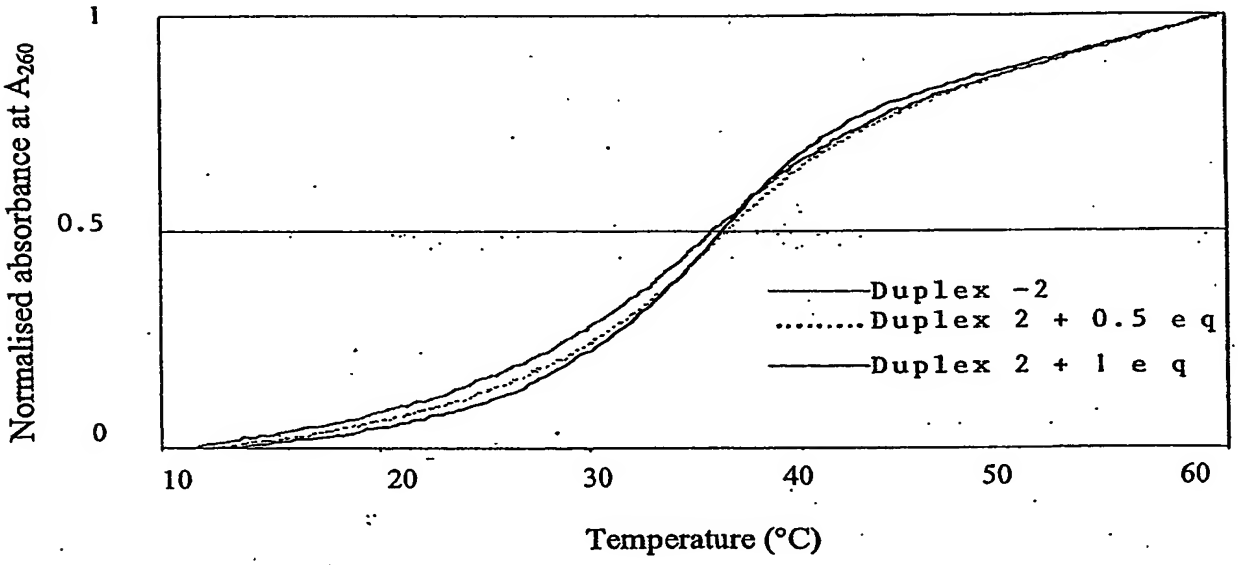

O2N
COOH
N
CH3
1
COOCH3
2
COCl
3
CONH
4
CONHCH2CH2NH
5a
6a
7a
CONHCH2CH2NH2
C
O
CH3

Figure 1


Normalised absorbance at A_{260}
1
0.5
0
10
20
30
40
50
60
Temperature (°C)
Duplex -1
Duplex 1 + 0.5 eq
Duplex 1 + 1 eq


Normalised absorbance at A_{260}
1
0.5
0
10
20
30
40
50
60
Temperature (°C)
Duplex -2
Duplex 2 + 0.5 eq
Duplex 2 + 1 eq

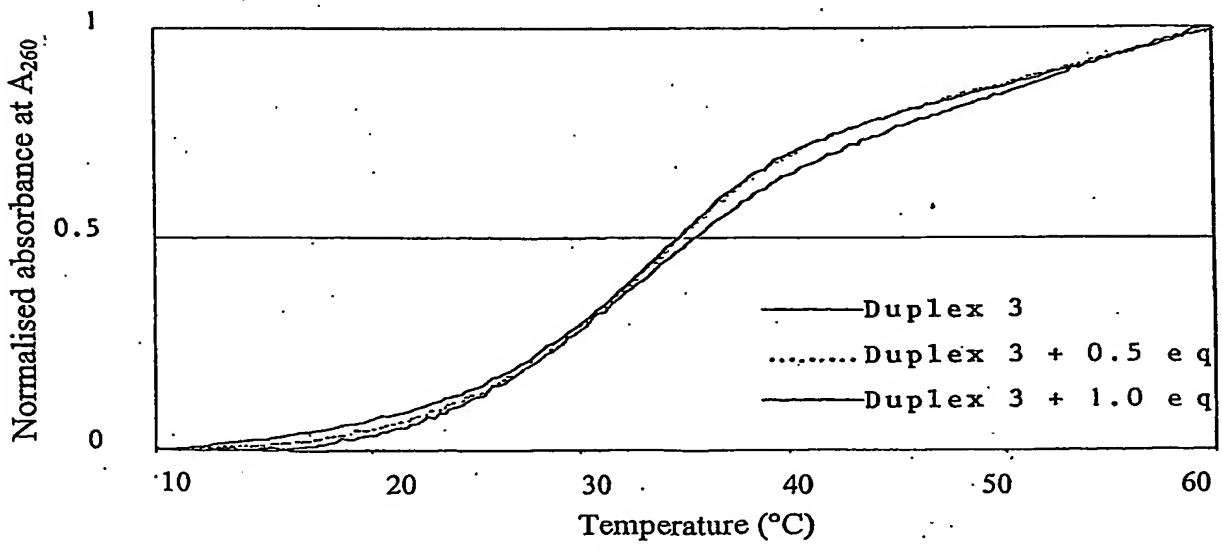

Normalised absorbance at A_{260}
1
0.5
0
10
20
30
40
50
60
Temperature (°C)
Duplex 3
Duplex 3 + 0.5 eq
Duplex 3 + 1.0 eq

Figure 2

CD titration Spectra

ICD titration Spectra

DJ1953-2 trans-Im/Py/Py-[CONH(CH_2)$_2$-NH_2)Pt(NH_3)$_2$Cl

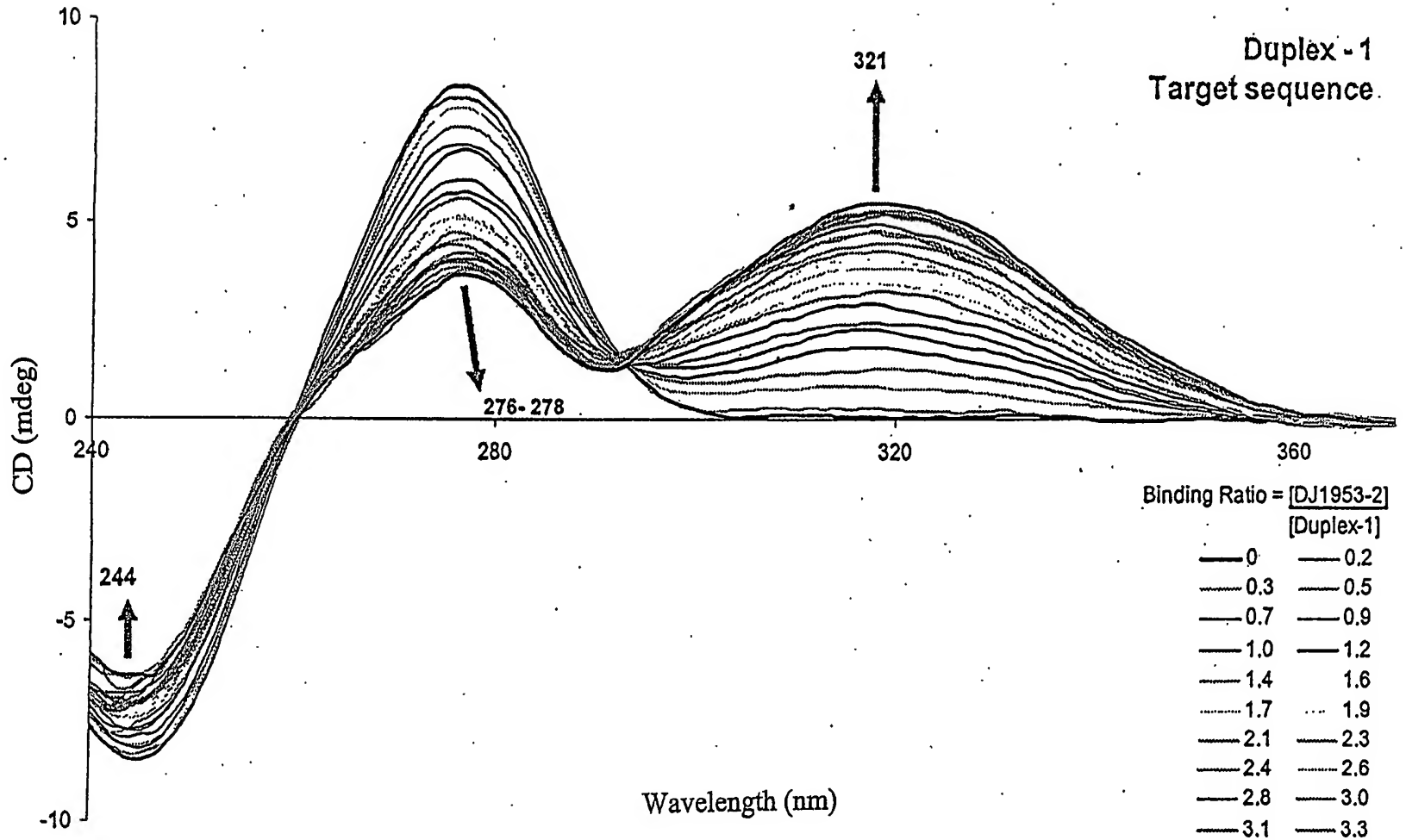


Figure 3(a)(i)

PCT/AU2004/001368
Received 14 December 2004

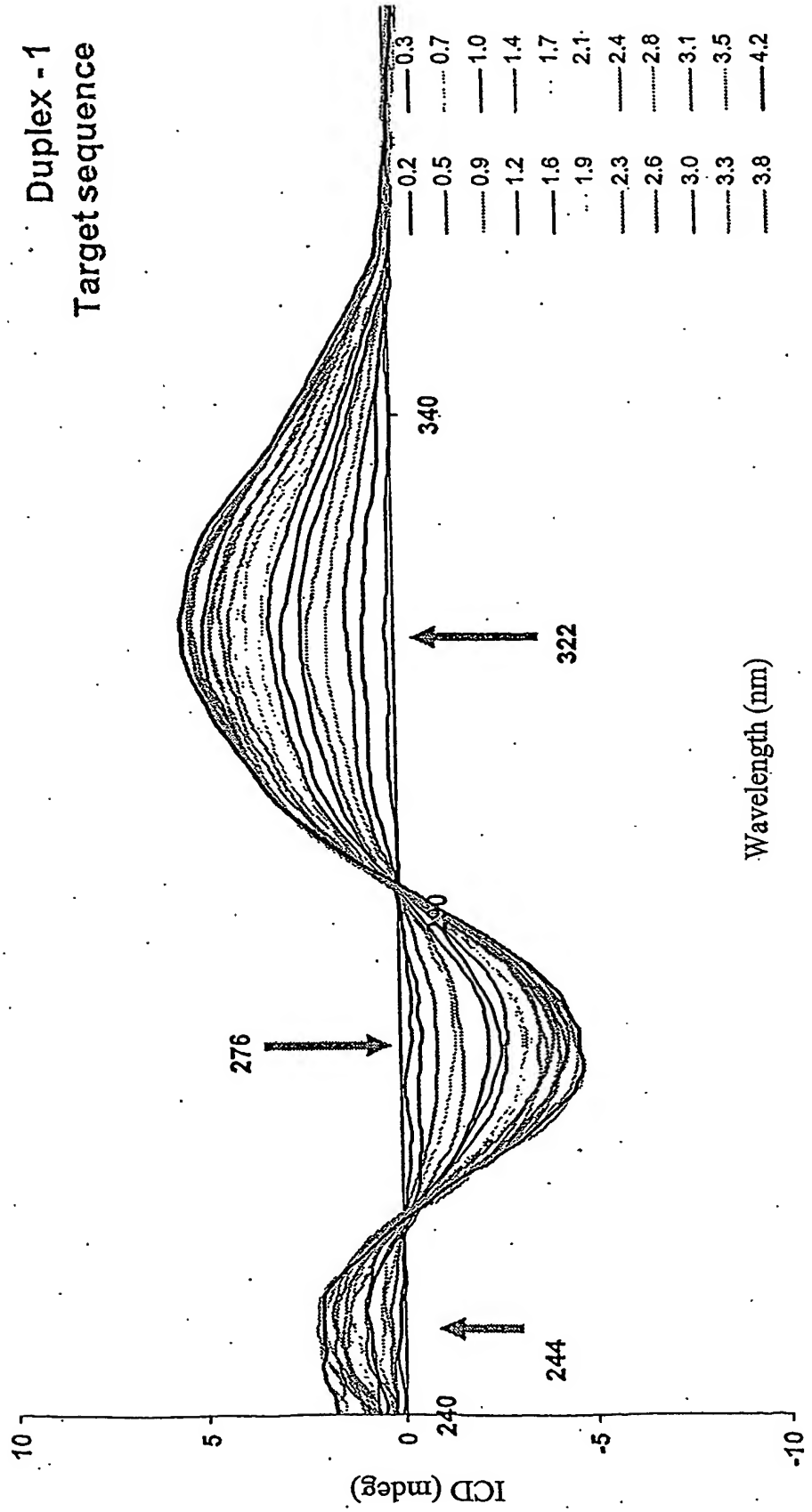

Duplex - 1
Target sequence
0.2
0.3
0.5
0.7
0.9
1.0
1.2
1.4
1.6
1.7
1.9
2.1
2.3
2.4
2.6
2.8
3.0
3.1
3.3
3.5
3.8
4.2
340
322
276
244
240
10
5
0
-5
-10
ICD (mdeg)
Wavelength (nm)

Figure 3(a)(ii)

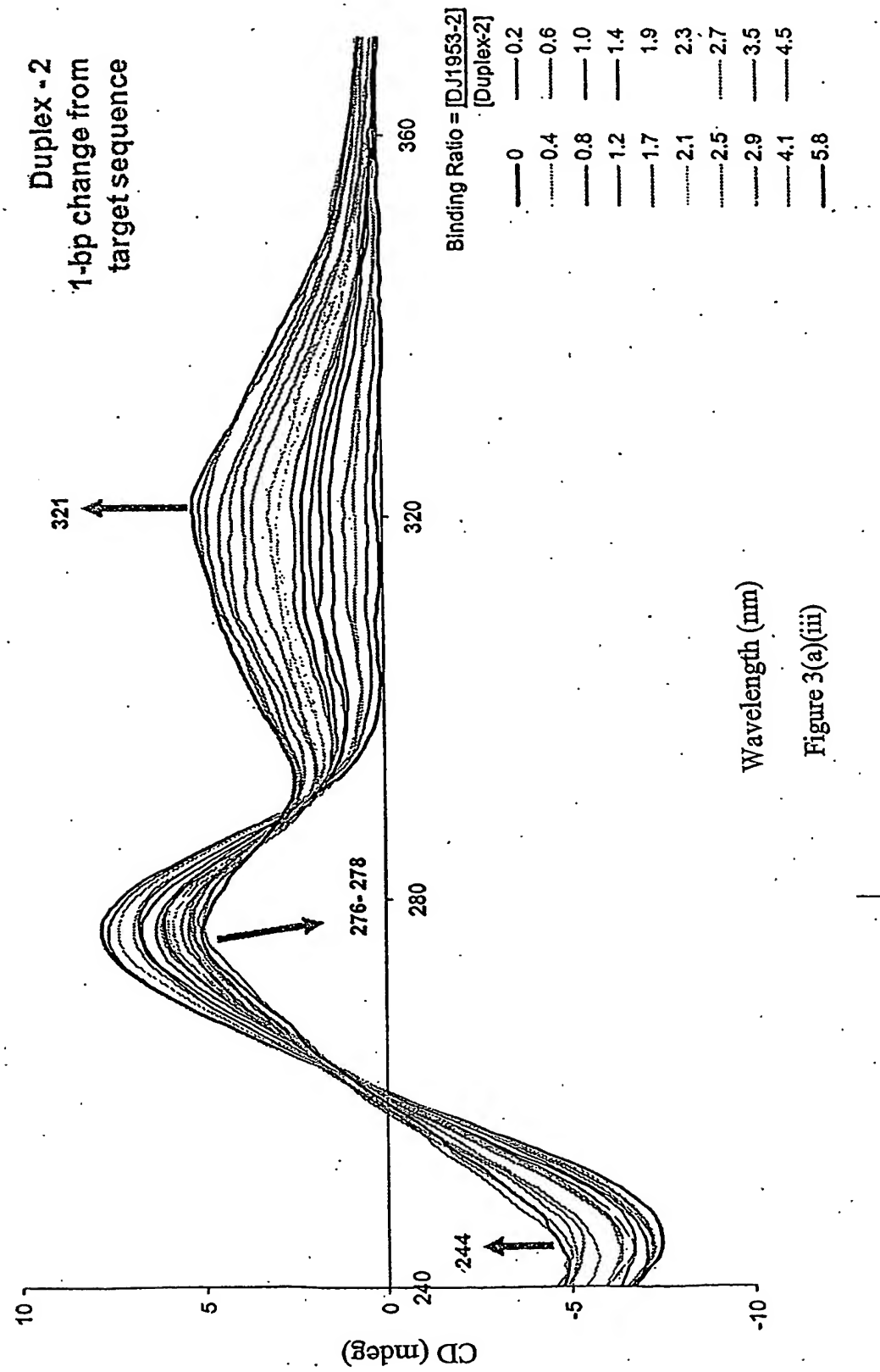


Figure 3(a)(iii)

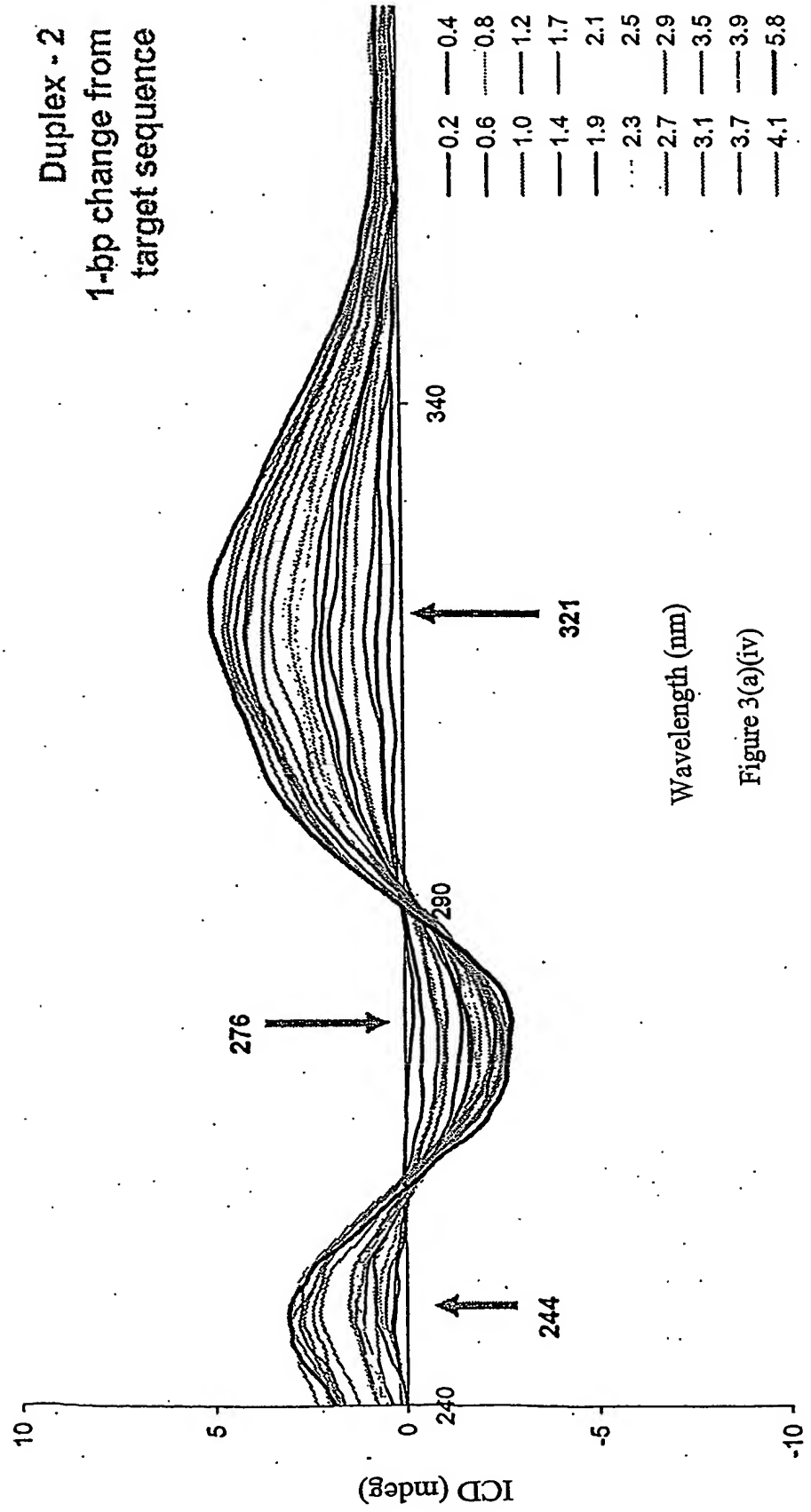

Duplex - 2
1-bp change from
target sequence
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.7
1.9
2.1
2.3
2.5
2.7
2.9
3.1
3.5
3.7
3.9
4.1
5.8
340
321
290
276
244
240
10
5
0
-5
-10
ICD (mdeg)
Wavelength (nm)

Figure 3(a)(iv)

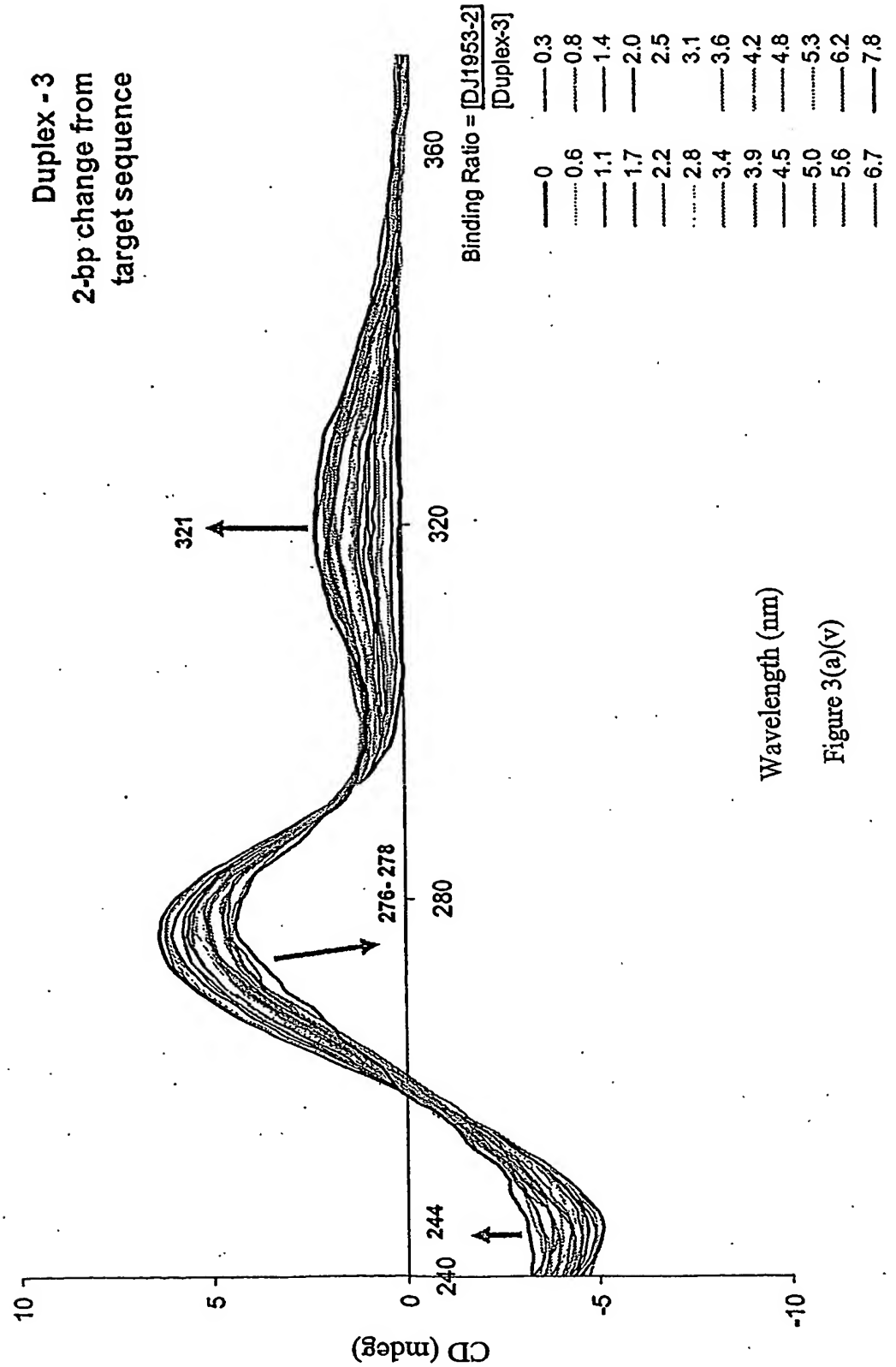

Duplex - 3
2-bp change from
target sequence
Binding Ratio = [DJ1953-2]
[Duplex-3]
0
0.3
0.6
0.8
1.1
1.4
1.7
2.0
2.2
2.5
2.8
3.1
3.4
3.6
3.9
4.2
4.5
4.8
5.0
5.3
5.6
6.2
6.7
7.8
321
276-278
244
240
360
320
280
10
5
0
-5
-10
CD (mdeg)
Wavelength (nm)

Figure 3(a)(v)

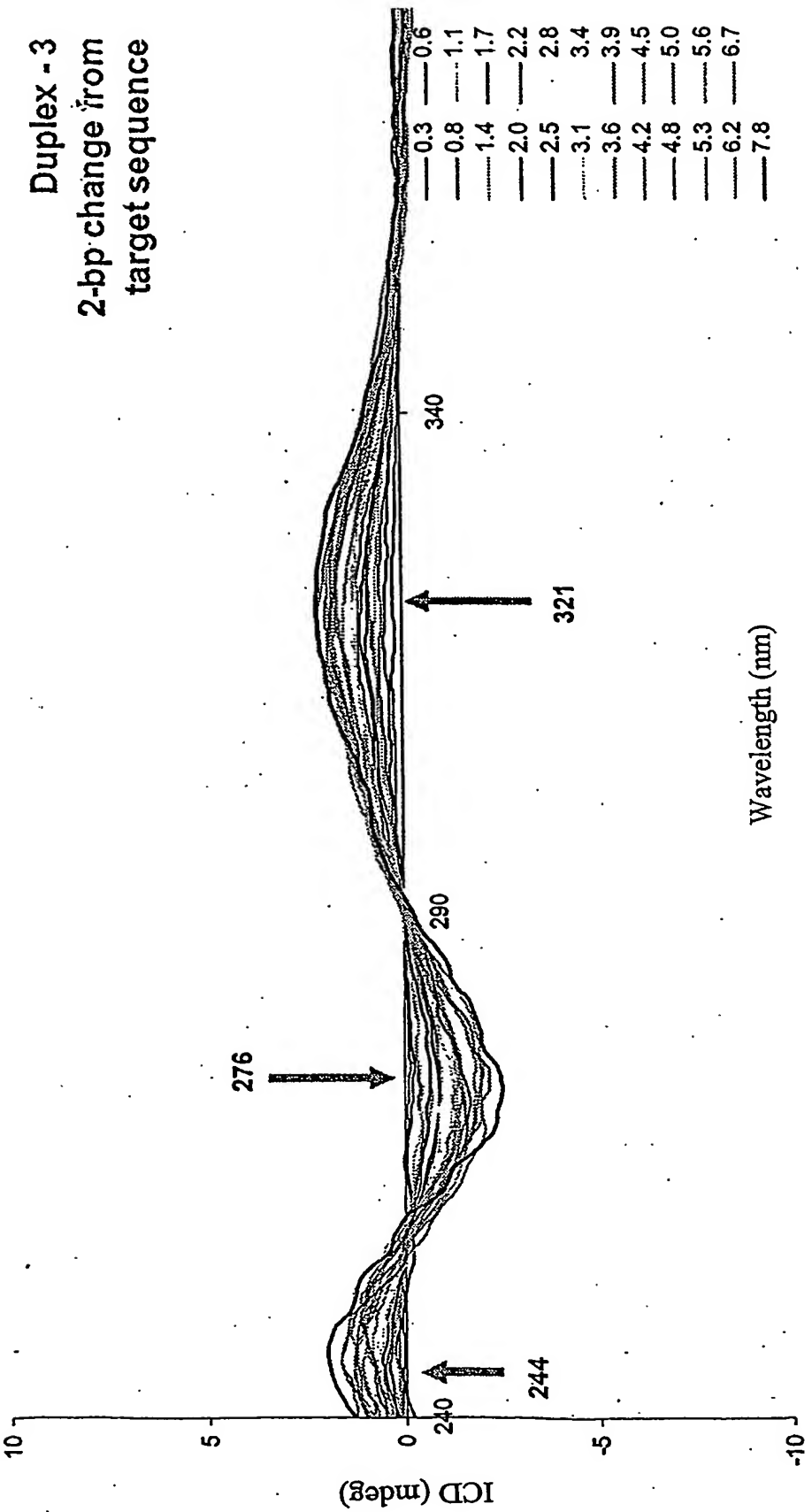

Duplex - 3
2-bp change from target sequence
0.3
0.6
0.8
1.1
1.4
1.7
2.0
2.2
2.5
2.8
3.1
3.4
3.6
3.9
4.2
4.5
4.8
5.0
5.3
5.6
6.2
6.7
7.8
340
321
290
276
244
240
10
5
0
-5
-10
ICD (mdeg)
Wavelength (nm)

Figure 3(a)(vi)

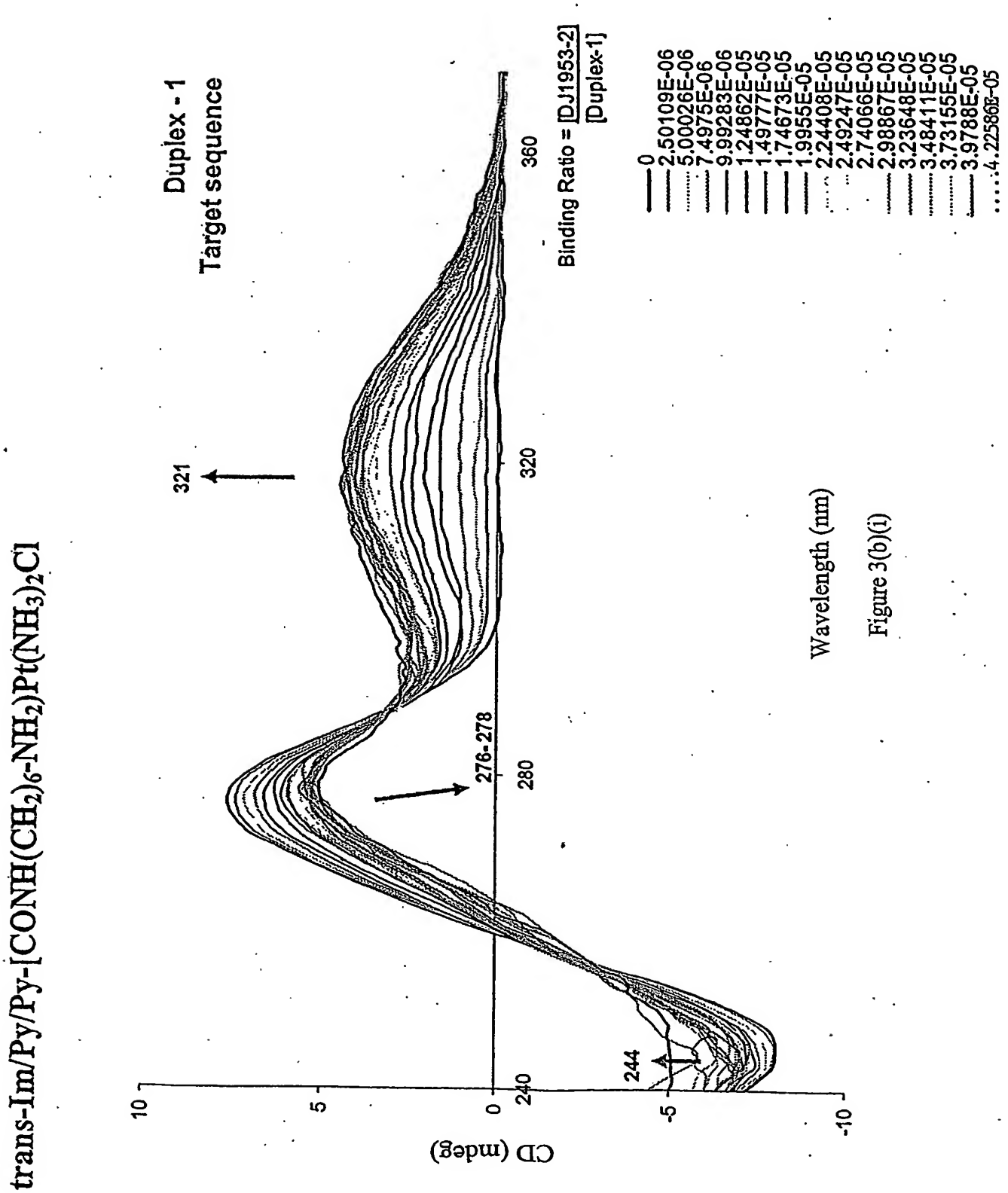

trans-Im/Py/Py-[CONH(CH2)6-NH2)Pt(NH3)2Cl
Duplex - 1
Target sequence
Binding Ratio = [DJ1953-2] / [Duplex-1]
0
2.50109E-06
5.00026E-06
7.4975E-06
9.99283E-06
1.24862E-05
1.49777E-05
1.74673E-05
1.9955E-05
2.24408E-05
2.49247E-05
2.74066E-05
2.98867E-05
3.23648E-05
3.48411E-05
3.73155E-05
3.9788E-05
4.22586E-05
321
276-278
244
240
280
320
360
10
5
0
-5
-10
CD (mdeg)
Wavelength (nm)

Figure 3(b)(i)

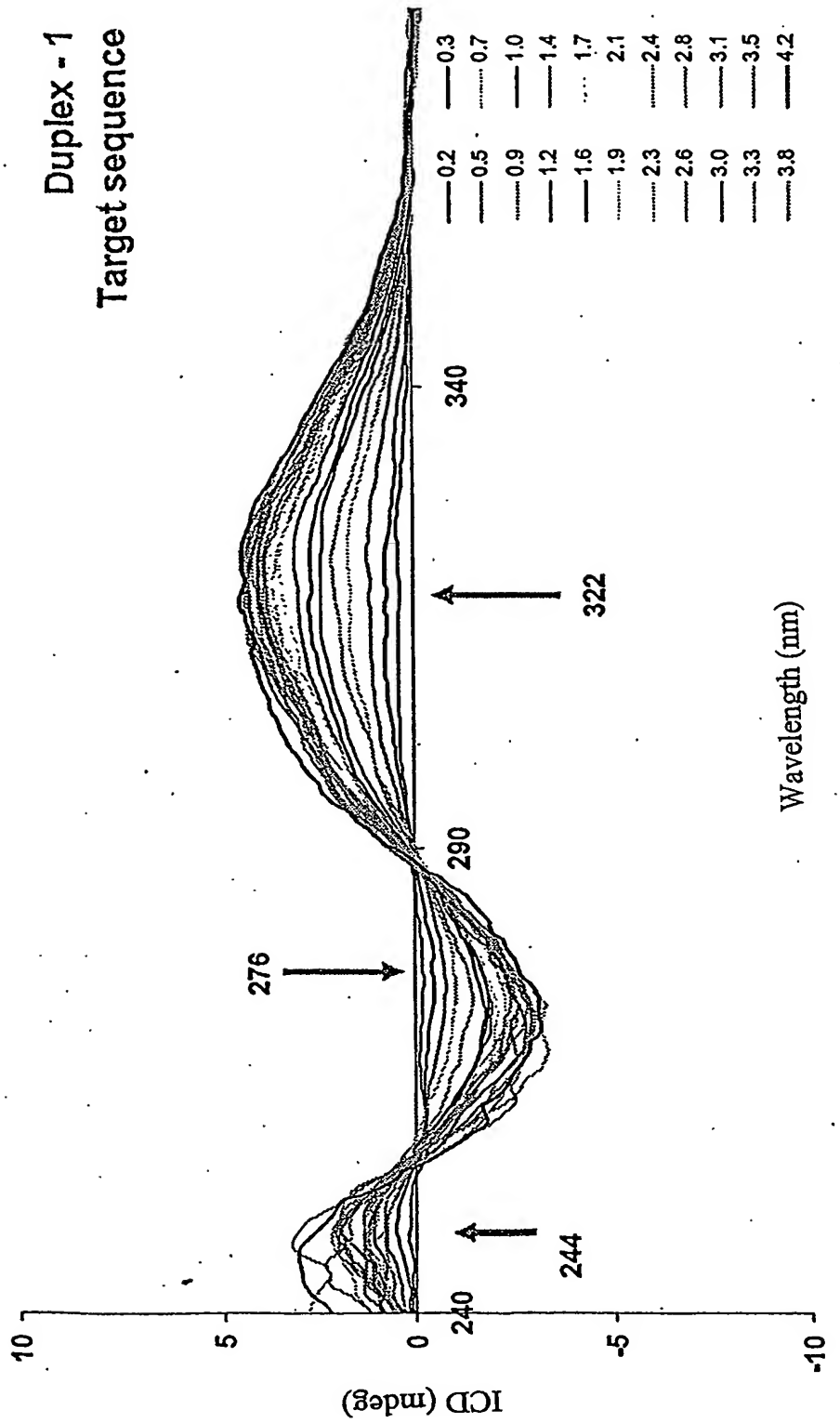

Duplex - 1
Target sequence
0.2
0.3
0.5
0.7
0.9
1.0
1.2
1.4
1.6
1.7
1.9
2.1
2.3
2.4
2.6
2.8
3.0
3.1
3.3
3.5
3.8
4.2
340
322
290
276
244
240
10
5
0
-5
-10
ICD (mdeg)
Wavelength (nm)

Figure 3(b)(ii)

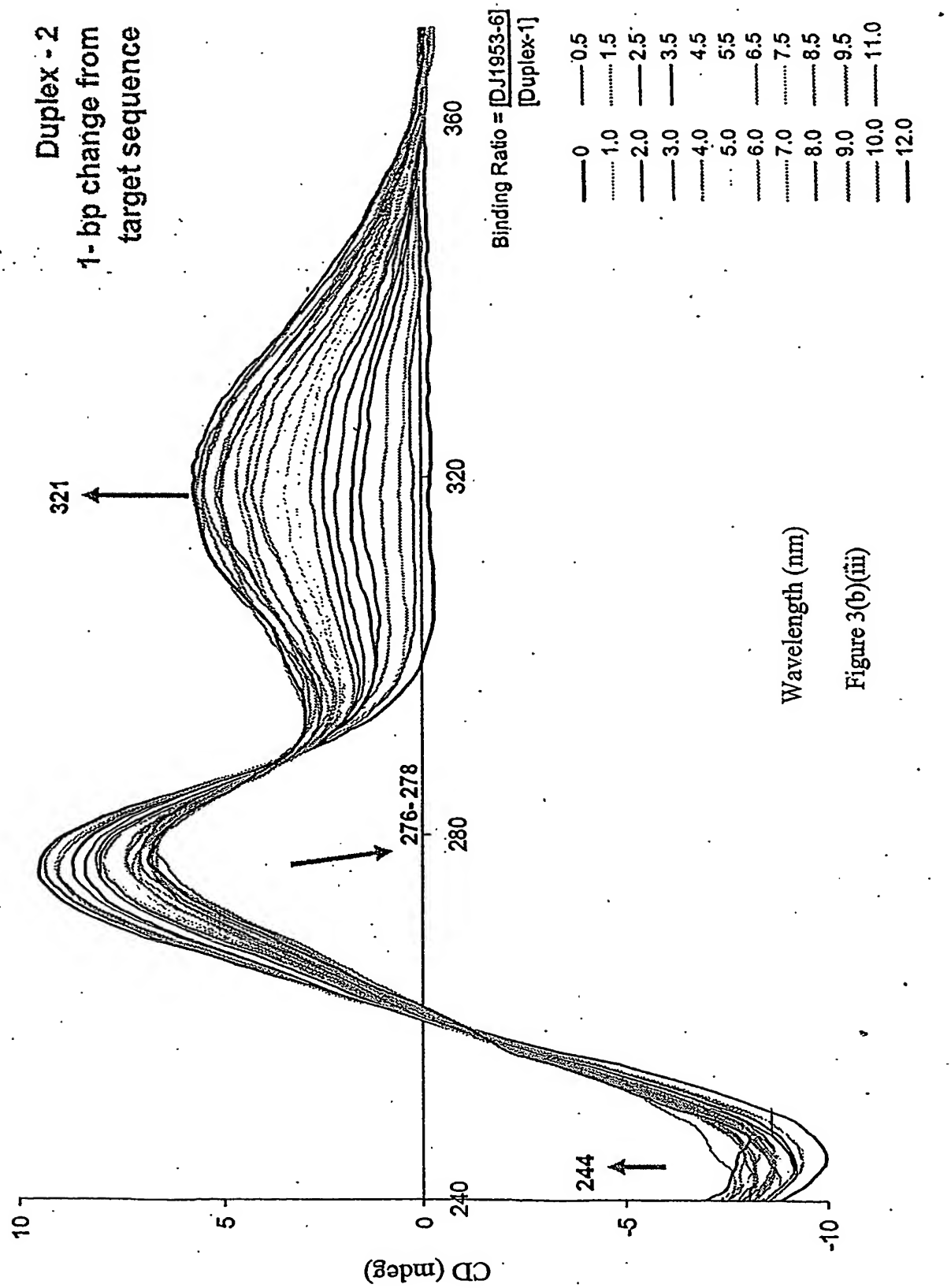


Figure 3(b)(iii)

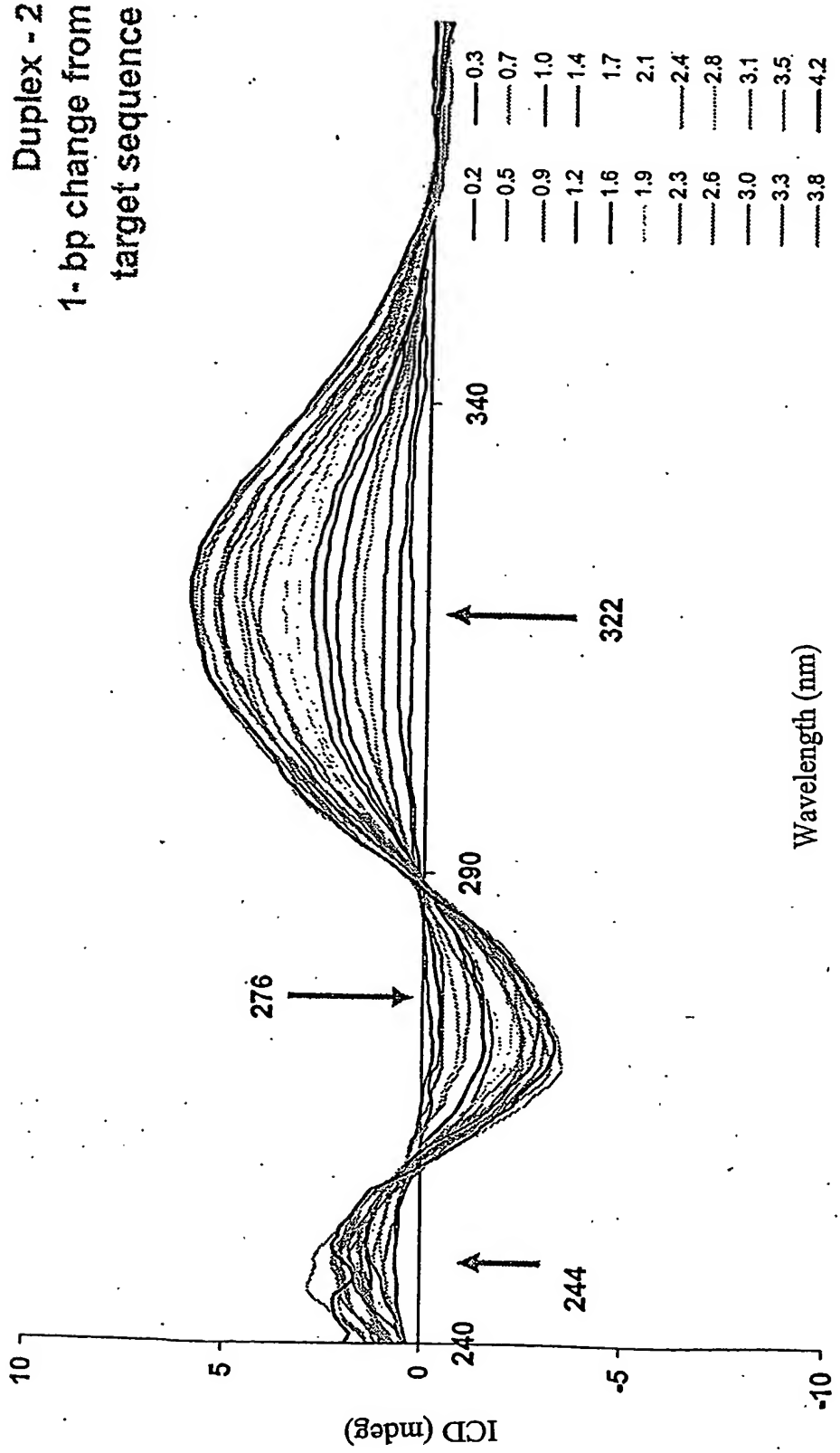

Duplex - 2
1- bp change from
target sequence
0.2
0.3
0.5
0.7
0.9
1.0
1.2
1.4
1.6
1.7
1.9
2.1
2.3
2.4
2.6
2.8
3.0
3.1
3.3
3.5
3.8
4.2
340
322
290
276
244
240
10
5
0
-5
-10
ICD (mdeg)
Wavelength (nm)

Figure 3(b)(iv)

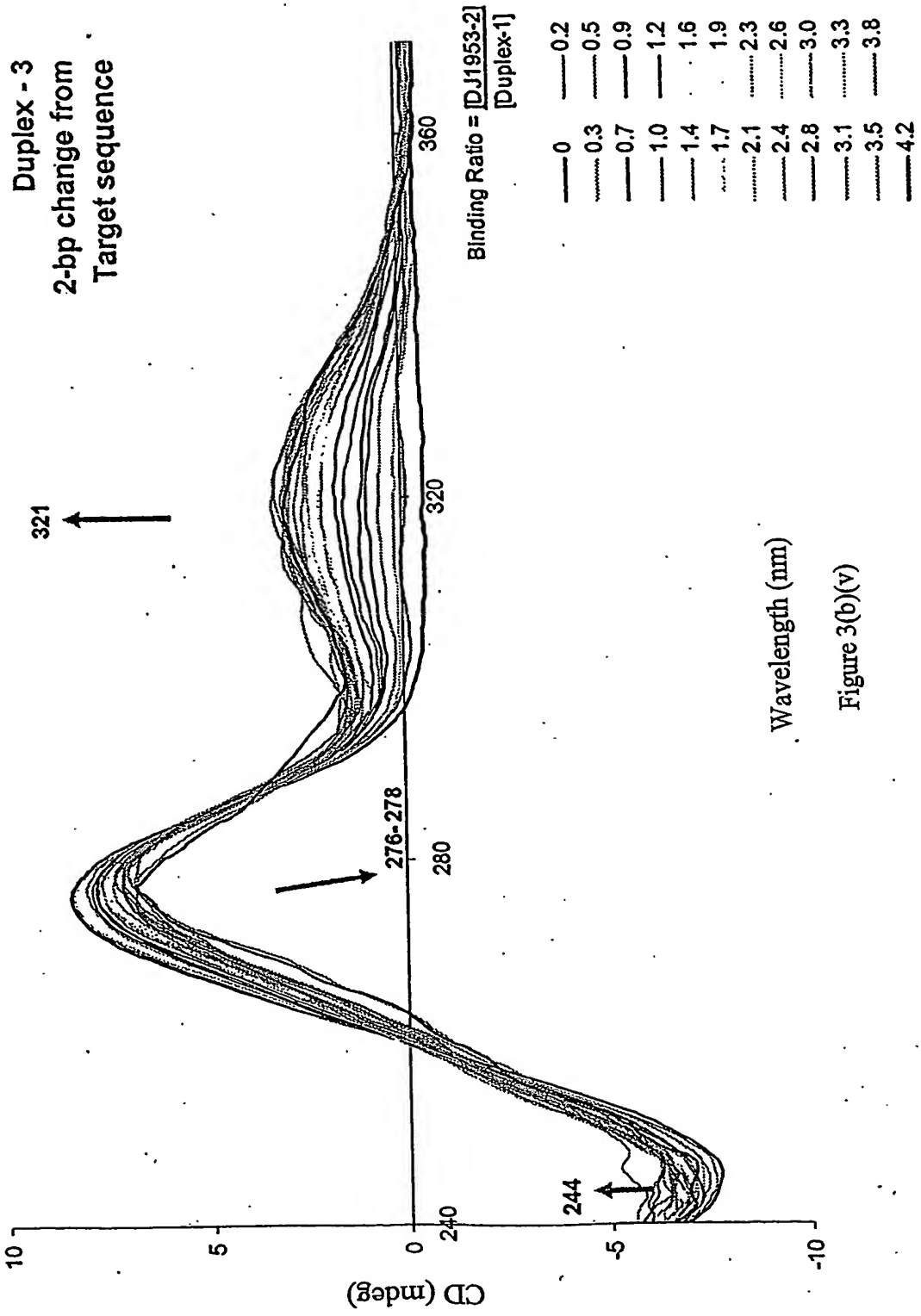

Duplex - 3
2-bp change from
Target sequence
321
276-278
244
240
280
320
360
10
5
0
-5
-10
CD (mdeg)
Wavelength (nm)
Binding Ratio = [DJ1953-2] / [Duplex-1]
0
0.2
0.3
0.5
0.7
0.9
1.0
1.2
1.4
1.6
1.7
1.9
2.1
2.3
2.4
2.6
2.8
3.0
3.1
3.3
3.5
3.8
4.2

Figure 3(b)(v)

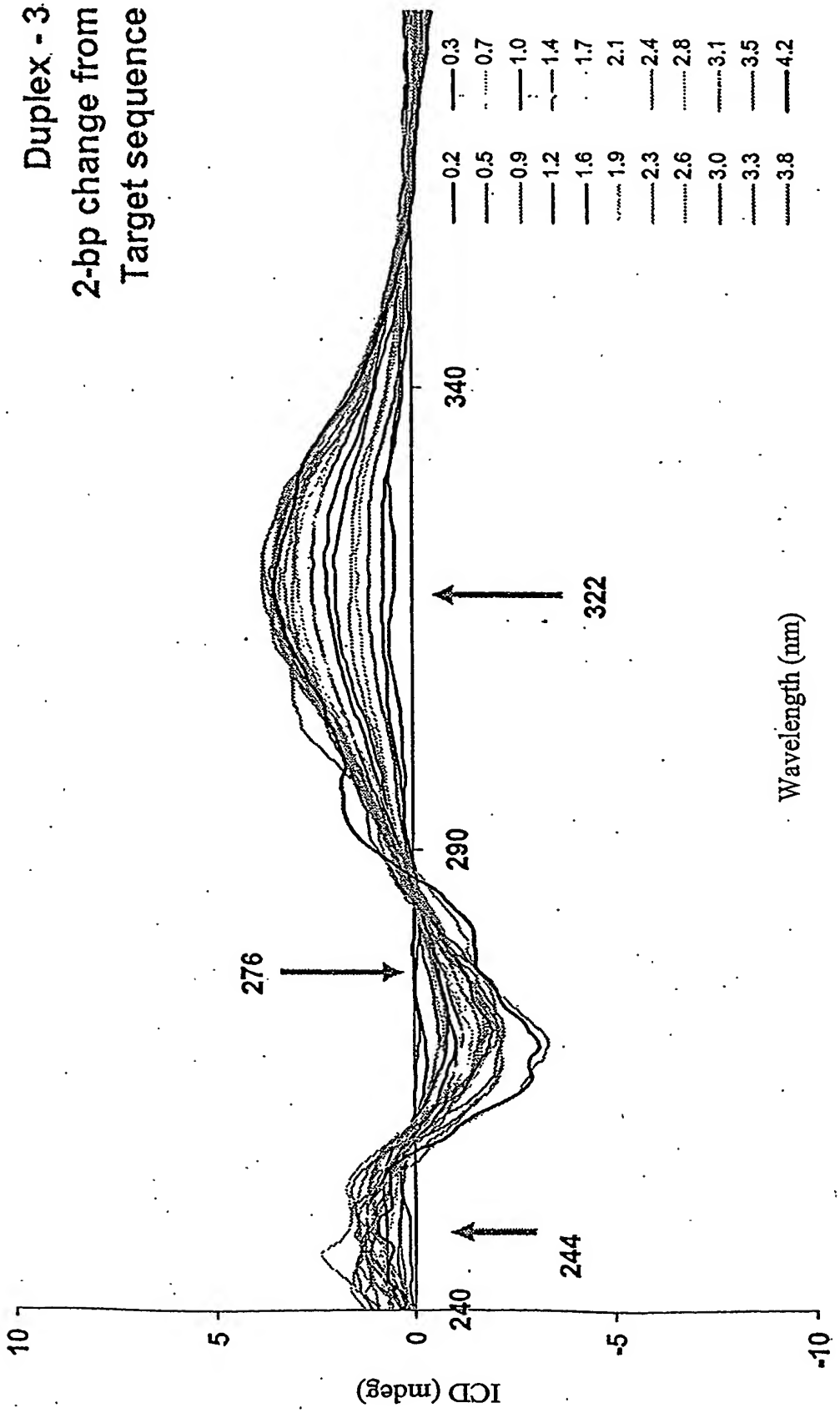

Duplex - 3
2-bp change from
Target sequence
0.2
0.3
0.5
0.7
0.9
1.0
1.2
1.4
1.6
1.7
1.9
2.1
2.3
2.4
2.6
2.8
3.0
3.1
3.3
3.5
3.8
4.2
340
322
290
276
244
240
10
5
0
-5
-10
CD (mdeg)
Wavelength (nm)

Figure 3(b)(vi)

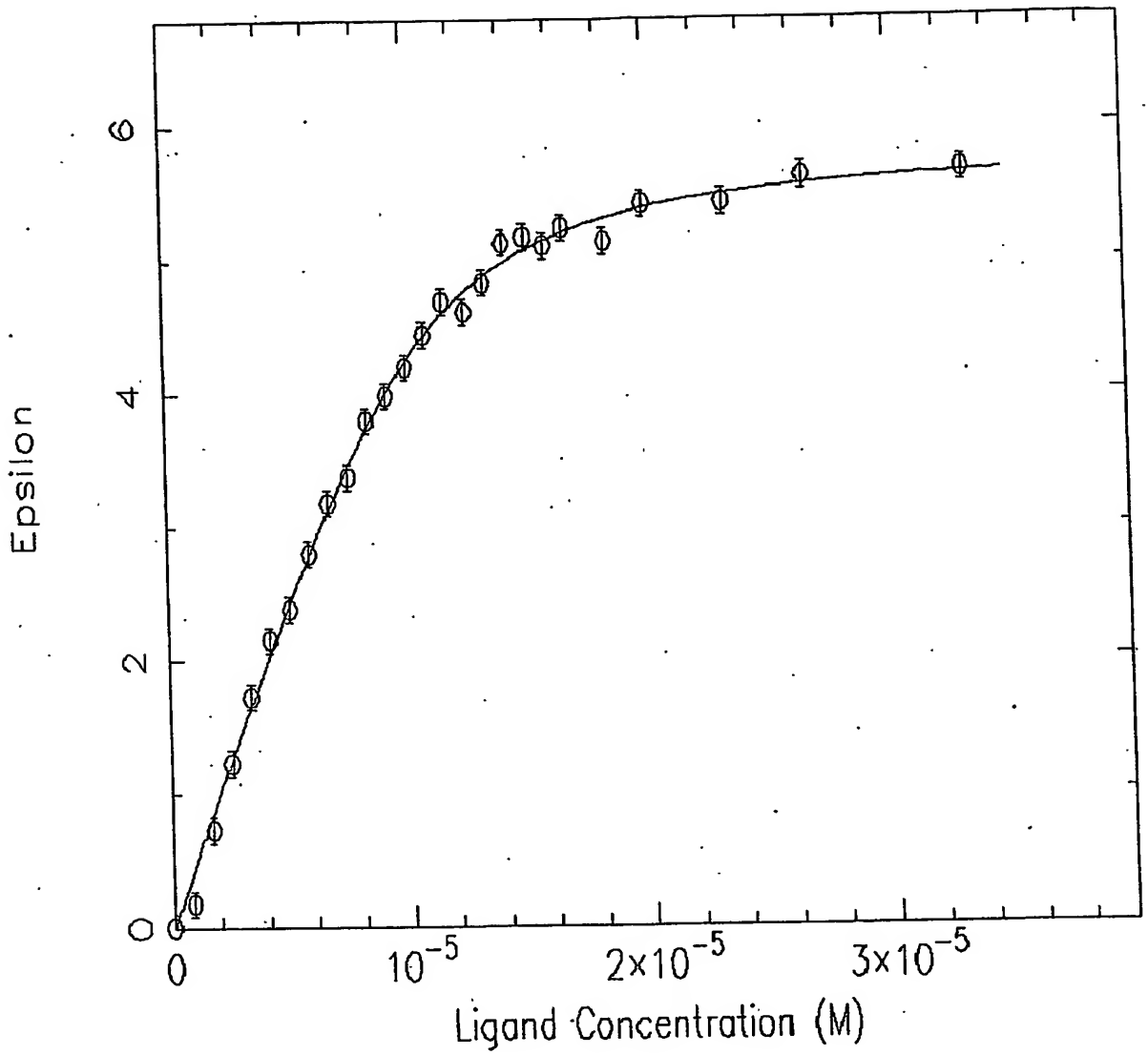

Epsilon
0
2
4
6
0
10^{-5}
2×10^{-5}
3×10^{-5}
Ligand Concentration (M)

Figure 3c

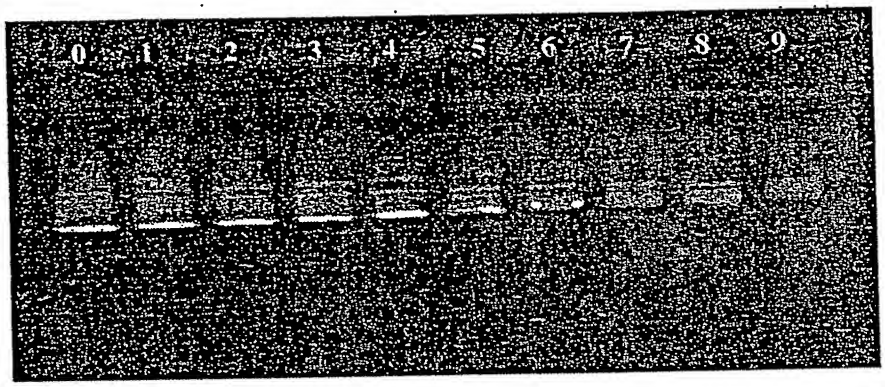


Figure 4

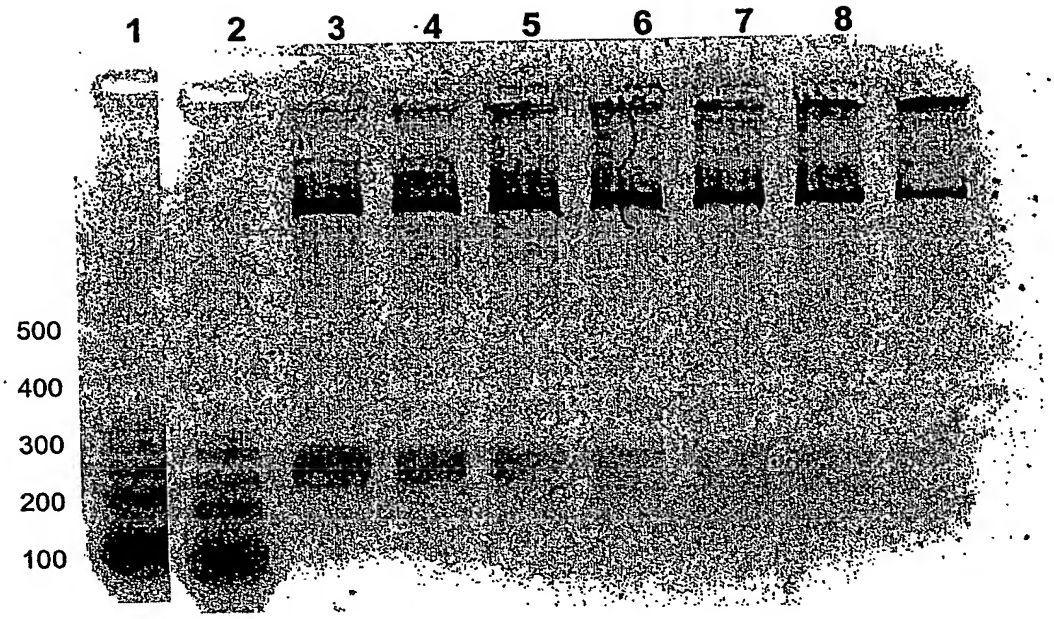


Figure 5

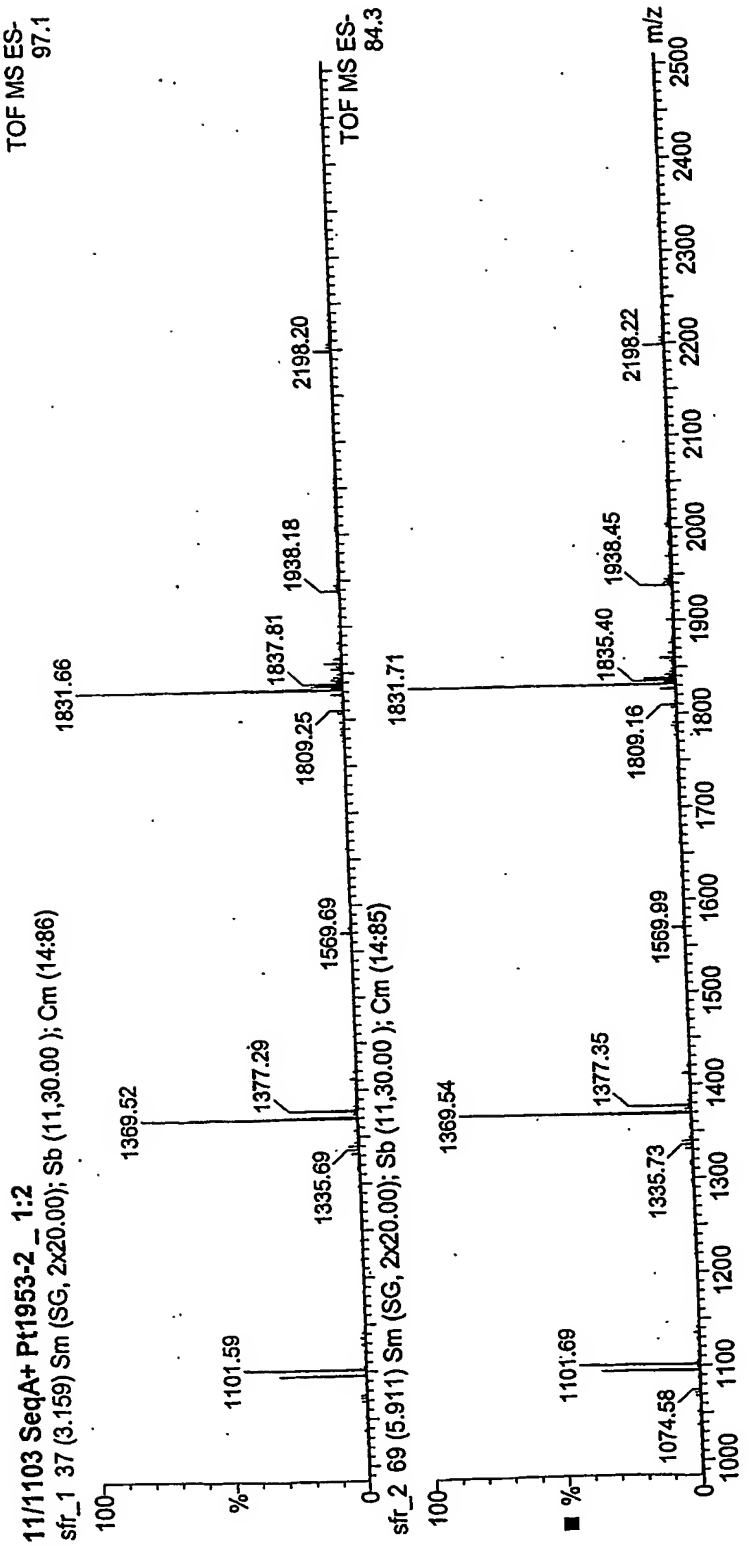

11/1103 SeqA+ Pt1953-2 _ 1:2
sfr_1 37 (3.159) Sm (SG, 2x20.00); Sb (11,30.00); Cm (14:86)
sfr_2 69 (5.911) Sm (SG, 2x20.00); Sb (11,30.00); Cm (14:85)
TOF MS ES- 97.1
TOF MS ES- 84.3
m/z
%
1831.66
1837.81
1938.18
2198.20
1809.25
1569.69
1369.52
1377.29
1335.69
1101.59
1831.71
1835.40
1938.45
2198.22
1809.16
1569.99
1369.54
1377.35
1335.73
1101.69
1074.58

Figure 6

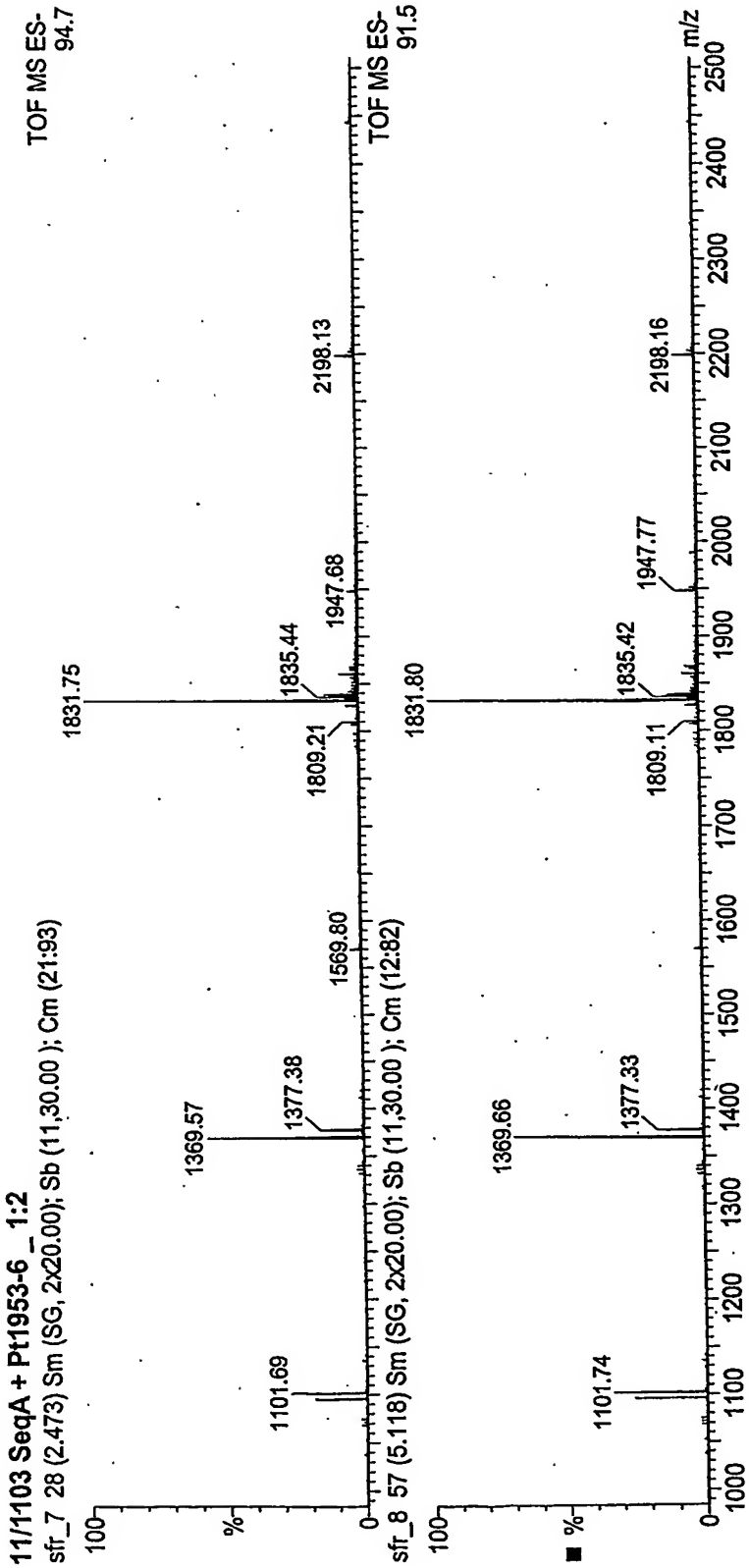

11/1103 SeqA + Pt1953-6 _ 1:2
sfr_7 28 (2.473) Sm (SG, 2x20.00); Sb (11,30.00); Cm (21:93)
TOF MS ES-
94.7
100
%
0
1101.69
1369.57
1377.38
1569.80
1809.21
1831.75
1835.44
1947.68
2198.13
sfr_8 57 (5.118) Sm (SG, 2x20.00); Sb (11,30.00); Cm (12:82)
TOF MS ES-
91.5
100
%
0
1101.74
1369.66
1377.33
1809.11
1831.80
1835.42
1947.77
2198.16
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000
2100
2200
2300
2400
2500
m/z

Figure 7